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Archives of Internal Medicine

VOL. 26 NOVEMBER, 1920 No. 5

HYPERSENSITIVENESS TO ARSPHENAMIN FOLLOWING EXFOLIATIVE DERMATITIS*

A CUTANEOUS TEST

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AND
EDWIN P. MAYNARD, JR., M.D.
NEW YORK

Following the use of arsphenamin or neo-arsphenamin in the treatment of syphilis, a variety of untoward reactions are frequently noted, some of which are well known to all who use this form of therapy and of very temporary moment; others, fortunately less frequent, are of far more serious consequence. These manifestations are sufficiently distinct in time of occurrence, nature and duration to have received special names, but all the types are easily confused and very frequently no attempt is made to differentiate them. It seems important, however, to do so, because very serious consequences may occasionally be avoided by an early recognition of signs which indicate the onset of one of the more serious types.

The most serviceable classification of these phenomena to be found in the recent literature is that of Sicard and Roger.[1] We have adopted this classification with certain modifications and our review of published cases, as well as observation of patients treated at the Presbyterian Hospital, has shown it to be simple and adequate. We recognize four types, with subdivisions of the third, dependent on the organ most manifestly injured:

1. Nitritoid crisis.
2. Herxheimer reaction.
3. Acute arsenic poisoning: (*a*) renal type; (*b*) hepatic type.
4. Chronic arsenic poisoning.

To this list might be added cases of simple overdosage or improper preparation of the drug, but as modern methods and knowledge have almost eliminated this group, we will not consider them here as responses to arsphenamin treatment. The four groups mentioned occur despite the most careful dosage and technic of administration.

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* From the Medical Clinic of the Presbyterian Hospital.

1. Sicard, J. A., and Roger, H.: Bull. et mem. Soc. méd. d. hôp. de Par. **13**:181, 1918.

It should be emphasized that, except for the nitritoid crises,[2] all of these reactions are of exceedingly infrequent occurrence, although we have no statistics of their relative incidence in a large series of cases.

The limits of this paper do not permit a detailed consideration of the first three types. The chronic arsenic poisoning cases are those in which we are especially interested because they are so severe in their manifestations and yet so insidious in onset, that we believe they may be avoided by due care in watching for early symptoms and by an adequate knowledge of the difference between these and the symptoms of the other types. We propose to present our case at this time and in the discussion to point out the characteristics of this form of poisoning.

REPORT OF CASE

History.—Mrs. G. L., aged 43 years, was admitted to the Presbyterian Hospital May 16, 1919, for antisyphilitic treatment on learning that her husband was a syphilitic, suffering from general paresis. Eight years before she had had a sudden paralysis of the left arm and leg and the right side of the face with some involvement of speech. This condition completely cleared up in one year.

Physical Examination.—The general physical and neurologic examination on admission showed Argyll Robertson pupils, atrophy of the muscles of the left leg and thigh, unequal knee jerks, the left greater than the right, a left exhaustible ankle clonus, left patellar clonus, left Babinski and confirmatory reflexes.

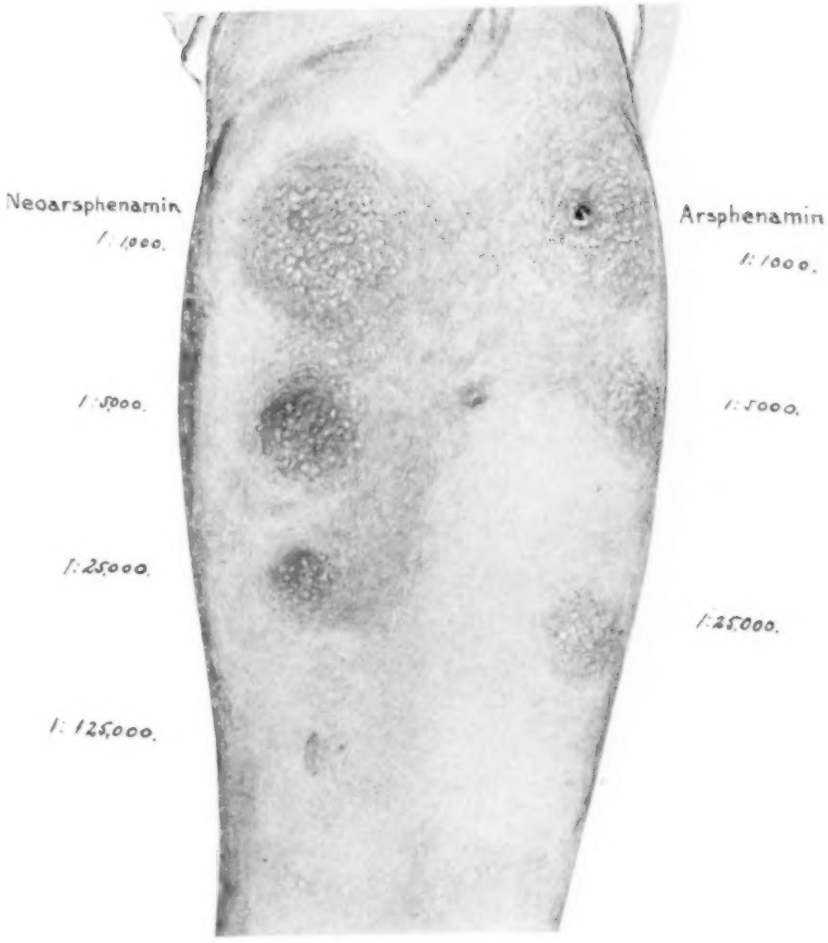
Laboratory Examination.—The blood Wassermann was: alcoholic antigen ++++, cholesterin antigen ++. The spinal fluid Wassermann was: alcoholic antigen, +++ in 0.2 c.c.; cholesterin antigen, +++ in 0.6 c.c. The colloidal gold curve was: 5555544210. There were 91 cells per cm. in the spinal fluid, 91 per cent. lymphocytes and 9 per cent. polymorphonuclears. Globulin, ++.

Treatment.—On the basis of the laboratory data, antisyphilitic treatment was begun at once. Mercury bichlorid, 1 grain, was given intramuscularly at intervals of a week for three doses, and at the same time potassium iodid, in three courses, to a total of 2,365 grains by mouth was given. After the second mercury injection, intravenous arsphenamin was begun. The patient received six intravenous treatments, one a week, the dosage being 0.2, 0.3, 0.4, 0.4, 0.4, 0.4 gm., respectively. There was no reaction of any kind following these intravenous treatments.

The fourth intravenous treatment was combined with an intraspinous injection, using the Swift-Ellis technic without reinforcing the serum. This caused some pain and soreness in the lumbar region, radiating down the legs. The sixth intravenous treatment was also combined with an intraspinous injection and was followed by the same pain in the lumbar region and legs. This time, however, the pain grew worse until walking became very difficult. The urine was definitely bloody on two occasions.

The patient was readmitted five days after the treatment with very definite signs of meningeal irritation; a stiff neck, double Kernig and fever. The spinal fluid showed an increase in pressure and was sterile. A bloody tap made cell count and globulin estimation impossible. A blood culture was sterile and there was no leukocytosis. The urine showed only a very faint trace of albumin and no red blood cells or casts. The temperature gradually reached normal in

2. Berman, L.: Arch. Int. Med. **22**:217 (Aug.) 1918.



The cutaneous reactions seventy-two hours after injection of arsphenamin and neo-arsphenamin in varying dilutions.

Illustrating Article by Harold C. Stuart, M.D., and Edwin P. Maynard, Jr., M.D.
New York, Archives of Internal Medicine, November, 1920

one week and the signs of meningeal irritation slowly cleared up. The picture was thought to be that of a sterile leptomeningitis due to the introduction of serum into the spinal canal.

Twelve days after admission, the patient was given her seventh dose of arsphenamin, 0.4 gm. This was immediately followed by severe sharp pain over the sacrum and down the legs which disappeared during the night. There was also some erythema on the back of the left wrist and urticarial spots on the left deltoid. The next day she had a fine, itching, erythematous rash on the wrists and shins which was relieved by epinephrin. This lasted two days and was considered to be an urticarial phenomenon, part of a mild nitritoid crisis.

One week later another 0.4 gm. of arsphenamin was given, making eight doses in nine weeks and three days. The treatment was followed in one hour by vomiting and transitory headache. The next morning there was definite swelling of the hands, forearm and feet, most marked in the left hand with slight redness and severe itching. The urine showed only a very faint trace of albumin and no red cells or casts.

Second Admission.—The patient was discharged but returned four days later because the swelling had rapidly progressed until it involved all the extremities, the chest, face and neck. There had been slight nausea and weakness, and the urine output had noticeably decreased.

Physical Findings.—On admission, the temperature was 98.8 F., pulse 84, and respirations 20. The face was swollen and of homogeneous dull red color without cyanosis. The eyelids, particularly the upper, were puffy, and there was slight conjunctival congestion and lacrimation. The nose showed a mild coryza, but the mucous membranes of the mouth showed no changes. Over the arms and legs was a diffuse erythema made up of small red areas, nearly confluent. The skin was dry, warm and rough, with a fine, branny desquamation. Pressure caused pain. The erythema extended to a lesser degree over the entire trunk, including the abdomen, being most marked in the dependent portions of the body. There was marked swelling of the hands, forearms, arms and legs, with a peculiar induration and pitting edema. There was some edema beneath the skin of the neck, anterior chest and back. The lower extremities presented marked vasomotor paresis, becoming a deep red when they hung in a dependent position.

Laboratory Findings.—There was a marked polymorphonuclear leukocytosis. The leukocytes numbered 20,000; polymorphonuclears, 87 per cent., of which 35 per cent. were eosinophil. The phthalein excretion was 39 per cent. in two hours. Blood pressure, 104/80. Urine: sp. gr., 1.014; albumin, negative. Sugar: negative; no casts or erythrocytes. Chlorids, 4.4 gm. per liter.

Clinical Course.—The patient was in the hospital two months and seven days. The skin manifestations dominated the picture. The erythema became a homogeneous dull red, edema was marked and the desquamation became generalized, the dead epithelium pulling off in large flakes. The skin showed a tendency to fissure wherever natural folds occurred, but very few denuded areas appeared. Profuse, sour smelling perspiration was a disagreeable feature. There was marked falling of the hair and the finger and toenails were in process of desquamation on discharge. Some erythema and skin exfoliation persisted and recurred in small areas even four months after the onset of the illness.

Bronchopneumonia was a serious complication. This occurred in the second week and subsided in four days. Perhaps the most alarming feature of the illness, however, was an acute nephritis that developed in the third week and did not begin to clear up until the sixth.

There was a marked obliguria, 190-550 c.c. of urine in twenty-four hours on a fluid intake of from 1,600 to 3,000 c.c. The blood urea was 0.44 gm. per liter, and the plasma carbon dioxid, 57.6 volume per cent. Urinalysis showed from a very faint trace to a trace of albumin with many hyalin casts. A phenolsulphone

Fig. 1.—The dermatitis at its height in the second week.

phthalein test was unreadable in one hour, because of discoloration of the urine and 10 per cent. at the end of two hours. The chlorid output was 2.7 gm. per liter. In the sixth week, the urine output rose to from 1,000 to 1,900 c.c.; no more casts were seen and the blood urea dropped to 0.21 gm. per liter.

The leukocyte count was very interesting in that there was a very marked eosinophilia during the height of the dermatitis. On one occasion, the white cells numbered 20,000, with 87 per cent. polymorphonuclear leukocytes, of which 35 per cent. were eosinophils. The leukocytosis and eosinophilia gradually diminished until during convalescence the count was: leukocytes, 8,500; polymorphonuclears, 61 per cent., with 1 per cent. eosinophils.

Other complications of the arsenic poisoning were a purulent conjunctivitis and deafness due to occlusion of the external auditory canal by desquamated epithelium. Peculiar trembling, chilly sensations were annoying and seemed to have no relation to adequate body warmth. They were relieved by baking. *B. pyocyaneus* was recovered from urine cultures and from axillary and pectoral abscesses that developed during the illness. The gastro-intestinal symptoms described in arsenic poisoning, i. e., nausea, vomiting and diarrhea, were never manifest.

Arsenic was found in the urine, by means of a modification of the Marsh test and persisted throughout the course, being present ninety-seven days after the last dose of arsphenamin.

Subsequent Course.—The patient has been seen four times since discharge, Oct. 21, Oct. 31, Nov. 28, 1919, and Feb. 1, 1920. Twenty-four days after discharge she complained of a slight transitory rash coming out first on the neck and arms. This appeared as tiny, red, itching elevations that became scaly and then disappeared. The skin everywhere was a little redder than normal and thickened in the folds. Seven weeks after discharge, she was still troubled with the occasional appearance of this rash. Otherwise she felt very well and weighed more than she had in twenty-three years.

Treatment.—The treatment was aimed at elimination of the arsphenamin and consisted in forcing fluids, colon irrigations and mild catharsis. Cold cream and boric acid ointment were used for the dermatitis.

DISCUSSION

It is of interest to note that this case of exfoliative dermatitis developed after the seventh dose of arsphenamin. The dosage had certainly not been excessive as it had never exceeded 0.4 gm., and the total amount was 2.5 gm. at the time the first rash appeared. The poisoning can be explained on the supposition that the patient belongs to that group of individuals that show a hypersensitiveness to arsenic or that there was an accumulation of arsenic in the tissues due to faulty elimination. There is some evidence for the second of these theories. First, the patient gave a history of bloody urine at the onset of the meningitis and an acute nephritis developed subsequently. Second, arsenic was present in the urine throughout the illness. It seems likely that the kidneys were primarily at fault. During the course of arsphenamin, they failed to eliminate the requisite amount of arsenic between treatments and the gradual accumulation of the drug resulted in an arsenical dermatitis and an acute nephritis.

The earliest signs of sensitiveness to arsenic are also extremely important. The irritative meningitis and hematuria that followed the sixth treatment may have been the first expression of this. At least,

it is fair to say that the serum produced a degree of irritation far beyond that usually seen after the Swift-Ellis treatment. The first manifestations in the skin came after the seventh dose of arsphenamin, when there immediately appeared some erythema on the back of the left wrist and urticarial spots on the left deltoid. The next morning there were very fine, itching, fairly discrete macules and papules on the wrists and shins, very probably a true arsenical dermatitis. Therefore any eruption occurring after the taking of arsphenamin, except the sudden blotchy urticarias that accompany a nitroid crisis, should be construed as an indication of sensitiveness to arsenic and a prolonged rest from treatment by arsphenamin should be given. If in addition to the rash, there is edema of the extremities with diffuse redness and itching, an arsenical dermatitis has already begun and all treatment by arsenic must abandoned for a time at least.[2a]

Cases of exfoliative dermatitis coming on after the intravenous use of arsenical preparations have been reported by Carr,[3] Malherbe,[4] Sicard and Roger,[1] Latham,[5] Evans,[6] Moore and Foley,[7] Didry[8] and Bine.[9] Mook,[10] while studying skin reactions to apothesin and quinin, tried to obtain a reaction to arsphenamin in a hypersensitive person by rubbing a solution of arsphenamin into a small scratch in the skin. This test was negative and constitutes the only recorded attempt to demonstrate hypersensitiveness by a cutaneous test. Sensitiveness to sodium cacodylate after one or more subcutaneous injections has been reported by Kauffmann[11] and Stäuble.[12] At the suggestion of Dr. W. T. Longcope, we have studied the local reaction excited by intradermal injections of varying dilutions of arsphenamin, neo-arsphenamin and other control substances in a series of twenty-six cases, in an attempt to find some means of foretelling which cases are hypersensitive to this preparation of arsenic, and, therefore, of possibly preventing such disastrous reactions. We were able to carry out these tests on the case reported above over eight months after the onset of the dermatitis, and we believe our results are of sufficient interest to warrant presentation at this time.

2a. Since the above was written French (Lancet **1**:1262, 1290) has reported several cases of exfoliative dermatitis in which he has resumed treatment cautiously with good results.

3. Carr, E. B.: Proc. Med. Ass'n C. Z. **10**:115, 1917.
4. Malherbe, H. (des Nantes): Ann. d. mal. ven. **12**:662, 1917.
5. Latham, J. R.: J. A. M. A. **73**:14 (July 5) 1919.
6. Evans, F. A.: Arch. Int. Med. **17**:1 (Jan.) 1916.
7. Moore, J. E., and Foley, F. E. B.: Arch. Dermat. & Syph. **1**:25 (Jan.) 1920.
8. Didry: Ann. d. mal. ven. **11**:723, 1916.
9. Biné, R.: Boston M. & S. J. **175**:96, 1916.
10. Mook, W. H.: Arch. Dermat. & Syph. **1**:651 (June) 1920.
11. Kaufmann: Deutsch. med. Wchnschr. **39**:272, 1913.
12. Stäuble: Deutsch. med. Wchnschr. **38**:242-245, 1912.

OUTLINE OF TESTS AND METHODS

The arsphenamin and neo-arsphenamin used in all tests were obtained from freshly prepared solutions about to be used in therapy, and corresponded exactly in sterility, neutrality and freshness to that used intravenously. These supplies were always made up in dilution of 0.1 gm. to 20 c.c. and further dilutions were made in sterile distilled water to give final dilutions of 1 : 1,000, 1 : 5,000, 1 : 25,000, 1 : 125,000, respectively. Dilutions of 1 : 200 were tried in the first few cases, but this concentration always produced a local irritation so that in subsequent tests it was not used. This irritation was occasionally met with after the injection of dilutions of 1 : 1,000, but the evidences of irritation were so delayed in appearance that they could not be confused with the reaction noted. A firm elevated nodule appeared in the skin at the site of injection after an interval of several days and increased in size and intensity until about the tenth to fourteenth day, then gradually disappeared after many weeks. These nodules would itch and occasionally show central necrosis.

As controls fifthieth-normal sodium hydroxid solution having an alkalinity greater than that of the arsphenamin, was used in most cases, but simple distilled water or physiologic sodium chlorid solution were used in a few. Others were also tested with sodium cacodylate as an arsenic containing control.

The technic of administration was to introduce into the superficial layers of the dermis sufficient solution to create a swelling from 3 to 4 mm. in diameter. The forearm was sterilized with alcohol and a sterile tuberculin syringe was employed. The various substances were thus introduced 3 inches apart along the volar aspect of the forearm and a chart of their distribution was kept for recording purposes. An attempt was made to make observations one-half hour, six hours, twenty-four hours and forty-eight hours after injection, and if any reaction appeared this was observed on subsequent days. This schedule could not be followed in detail in all cases tested, as some were dispensary patients; but in no case was the reaction called negative unless observations had been made for at least forty-eight hours after injection. Furthermore, many of the controls were performed on members of the house staff, who could be followed closely and who were able to supplement our readings by frequent examinations themselves.

The twenty-six cases which have been examined by this method can be divided into four groups:

1. Syphilitics treated with arsphenamin, developing severe exfoliative dermatitis; three cases.

2. Syphilitics treated with arsphenamin and having had no reaction or only immediate and temporary nitritoid reactions; seven cases.

3. Syphilitics having never received arsphenamin; six cases.

4. Nonsyphilitics and untreated controls; ten cases.

In the greater number of these cases, there was an immediate blotch of erythema surrounding the injection, just as constant in the control as in the test injections and fading within a few minutes or hours. There was also a minute papule or macule at the sight of inoculation, which would persist sometimes two or three days. This was usually a little more marked about the sodium hydroxid injection than about the other injections. The more marked reactions met with about the stronger dilutions of arsphenamin have been mentioned. All these were considered normal responses to local irritation and only cases showing these reactions were considered to be negative.

On this basis our results showed that all cases falling into groups two, three and four, that is twenty-three controls, were negative. In the first group we placed the case reported above, a case referred to the Presbyterian Hospital by Dr. J. A. Fordyce three months after a moderately severe exfoliative dermatitis, occurring during a first course of arsphenamin therapy, and a third referred from the Vanderbilt Clinic nine months after a generalized exfoliative dermatitis. The latter patient had suffered from a scaly eruption of the scalp and to a less extent of the body for many years before treatment had been begun. He had received course after course of arsphenamin over a period of years, and was away on a vacation without having received any of the latter drug for over a month when his extensive dermatitis appeared. It was, however, the concensus of opinion at the Vanderbilt Clinic, that this was a true arsphenamin dermatitis.

In the first two cases, we obtained very definite and quite similar reactions, varying only slightly in intensity. We had an opportunity of repeating the tests and following more closely the case reported herewith, and, therefore, we shall describe the reactions which followed these injections.

The patient was tested at five months and again at eight months after the onset of her dermatitis, and both times she showed a very unusual local reaction. It did not, in any particular, simulate the urticarial phenomena met with following the injection of foreign proteins, nor did it appear like the local necrosis produced even in controls by too concentrated solutions of arsphenamin. From six to eighteen hours after the injections, there appeared about the dilutions of 1:1,000, of both arsphenamin and neo-arsphenamin, a central elevated and finely indurated nodule about the size of a dime, dark red in color and itching intensely, surrounded by an outer zone three inches in diameter, rather whitish near the center, but quite red toward the

periphery. This outer margin was irregular, very slightly elevated and appeared even at this stage to be composed of minute papules united by an erythema, giving the appearance of goose flesh. Similar patches, diminishing in size, appeared about the greater dilutions down to the dilution of 1:125,000, which showed only a very small patch, not larger than the original injection.

At twenty-four hours, all the patches had become redder, and at forty-eight hours, the "goose-flesh" nature of the surface had become more pronounced and the distinction between inner and outer zones was less marked. At this time there was slight moisture over the strongest dilutions, but at all other times the reactions were dry. By the third day, all had diminished somewhat in size and showed quite rough surfaces and the edges were more irregular and formed by small discrete and firm papules.

On the fourth day after the intradermal tests, the patient felt nauseated and had severe pain in the lumbar region similar to that experienced after the intraspinous treatments. These persisted for about four weeks and then disappeared. There were no vomiting, lancinating pains or urinary disturbances and it seems hardly probable that the minute amount of arsenic injected could account for the disturbance. The skin reactions remained about as described for eleven days and then rapidly subsided.

Five weeks after the tests were performed, there were faint pink scaling spots at the sites of the injections of neo-arsphenamin in dilutions of from 1:1,000 to 1:25,000, likewise small red papules, diminishing in size from the same dilutions of arsphenamin. Itching was the only subjective symptom throughout. No reaction appeared at any time about controls of sodium hydroxid or sodium cacodylate. The second patient was tested three months after her dermatitis. The reaction was first noted at twenty-one hours and the patches never became as large, but the process had similar characteristics. They were still present when the case was last seen one week after the injection, the color having become a little browner and the surface showing a few fine scales. No reaction was noted about the controls of sodium cacodylate or physiologic sodium chlorid solution. The dilutions of neoarsphenamin were not used in testing this case.

The third case showed absolutely no reaction to either the arsphenamin or neo-arsphenamin test solutions or to the controls during the nine days over which he was followed.

The reaction met with in the first two cases seemed to be entirely too definite to be interpreted as anything less than a hypersensitiveness to some constituent of the arsphenamin preparation, present for from three to eight months after an extensive exfoliative dermatitis. This

hypersensitiveness was not found in a third case nine months after the dermatitis. We are unable to explain this, except on the ground that the hypersensitiveness, developed during the courses of therapy, had worn off during the nine months of freedom from treatment in the last case. It may be that this patient could now tolerate further arsphenamin therapy, but more cases are necessary to establish the value of intradermal tests as a guide for therapy.

These considerations make it evident that more tests will have to be performed on cases that have recovered from an arsenical dermatitis at varying intervals after their exfoliation, before the reactions will become of any practical value; but we believe that the results thus far obtained show that intradermal injections of dilutions of arsphenamin may be an index of a latent susceptibility. The only object in reporting these findings before more definite conclusions have been drawn from them is that thereby the series of tested cases may be increased. It is a rare condition, and our contact with it has been very limited; but we are very anxious that as cases appear from time to time they shall be tested in the very simple manner outlined above.

SUMMARY

I. Reactions following arsphenamin or neo-arsphenamin therapy may be divided into four types:

1. Nitritoid crisis.
2. Herxheimer reaction.
3. Acute arsenic poisoning
4. Chronic arsenic poisoning.

II. A case of exfoliative dermatitis or chronic arsenic poisoning is presented. The first cutaneous manifestations were persistent itching, papular eruptions on wrists and shins. It is possible that the irritative meningitis following the preceding treatment may have been the beginning of the symptoms of hypersensitiveness.

III. Cutaneous hypersensitiveness to arsphenamin and neo-arsphenamin occurs in patients who have suffered from exfoliative dermatitis. This was demonstrated by typical skin reactions in two such patients by means of intradermal injections of minute dilutions of the drug, but could not be demonstrated in a third, perhaps because the tests were made nine months after the dermatitis when the hypersensitiveness had subsided. This supposition, if substantiated, would make the skin reaction of practical importance in determining when it is safe to renew arsphenamin treatment.

EPIDEMIC INFECTIOUS JAUNDICE AND ITS RELATION TO THE THERAPY OF SYPHILIS*

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WITH AN INTERPRETATION OF THE DUODENAL FINDINGS BY
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The present study of icterus which develops during antisyphilitic treatment was inspired by the following circumstance: A patient who had completed twelve injections of arsphenamin at our hands in September, 1917, returned for observation in July, 1918, with a history of having been severely jaundiced in May, about nine months after his last arsphenamin injection. He volunteered the statement that his jaundice had been associated with a severe attack of multiple arthritis which came on following a cold, and that his brother had had an even more severe attack of arthritis with jaundice at the same time. The brother had never had syphilis and had never been treated for it. Circumstances in other cases suggesting an acute infection and sporadic cases of catarrhal jaundice which have also come under our observation (one occurred in a member of our staff), have further aroused our interest.

Moreover, in the recent American and European literature reports and discussions have appeared of the apparently frequent occurrence of occasionally fatal jaundice, ascribed by the authors to syphilis or the administration of arsphenamin. We have, therefore, felt it worth while to analyze and record our experience with this complication. The analysis of our material presents, we believe, strong circumstantial evidence to the effect that while antisyphilitic treatment may have a predisposing influence, such therapy may have been of minor importance during the past two years. The major or exciting cause may be an infection of as yet unknown etiology, possibly a tardy manifestation of epidemic influenza.

From August, 1916, when the Section on Dermatology and Syphilis of the Mayo Clinic was organized, to July, 1920, seventy cases of jaundice have come under our observation excluding those definitely associated with carcinoma of the liver. During this period the department has had under observation approximately 5,200 patients with syphilis. A certain percentage of these patients have passed from observation since this study was begun so that it was necessary to

* Studies from the Mayo Clinic.

communicate with the patients by questionnaires. Inquiries were also sent to physicians under whose care certain of these patients had been during their absence from the Clinic. The incidence of jaundice in our cases from all causes, therefore, does not exceed 1.3 per cent. The proportions represented by these figures should be borne in mind in any attempt to compare our experience with that of others.

One of us (Stokes), speaking from the experience of the past seven years, can confidently say that jaundice is a relatively rare incident in the types of syphilis and the forms of antisyphilitic treatment with which he has been concerned. In particular, jaundice has been an exceedingly rare complication of the first two years' experience of the Section on Dermatology and Syphilology. Not more than six cases were observed during this period (1916-1918). The methods of treatment employed during the first two years (August, 1916, to August, 1918) differed in no important respect from the methods used during the last two years (August, 1918, to July, 1920). Accordingly, the abrupt occurrence of sixty-four cases of jaundice between August, 1918, and July, 1920, certainly suggests the operation of some factor other than arsphenamin or antispecific treatment in the abstract to account for so singular a distribution. Meirowsky's statistics, prepared for the Allegemeiner Aertzlicher Verein of Cologne, based on 225,780 injections of arsphenamin, neo-arsphenamin, and arsphenamin sodium show the complication to be rare. In this unprecedented series jaundice occurs once in each 2,000 injections of arsphenamin (0.89 per cent.) and once in 6,000 injections of neo-arsphenamin. This estimate exceeds that of our experience. Even on the basis of the Meirowsky figures the expectancy for the incidence of postarsphenamin jaundice on this service up to June, 1920, would not exceed fourteen cases (28,000 injections). Since the method of administration of arsphenamin has remained constant, or, if anything, has been definitely improved as our experience enlarged, there remains a margin of fifty-six cases of jaundice to be explained by other causes than treatment *per se*.

Special toxicity of the drug employed must be considered. We have used the Dermatological Research Laboratory brands of arsphenamin and neo-arsphenamin practically continuously for three years. The high reputation of these products and the fact that no other manifestation of a heightened toxicity of the drug has been associated with the jaundice throughout so long a period of observation seems to exonerate the drug. Considerable concrete evidence at least will be needed to show that the increased incidence of jaundice during the period from November, 1919, to March, 1920, is a function of the toxicity of this brand of arsphenamin during this particular period of its manufacture.

The Clinical Picture of the Group Before Jaundice Appeared.—The seventy patients who developed jaundice in the period from August, 1916, to June, 1920, included examples of every aspect of syphilis, and, in addition, four patients in whom it could be excluded with reasonable certainty. Two of these patients had tuberculous glands, one had actinomycosis of the cecum, and one had indefinite symptoms for which he received a therapeutic test with negative results. Fifty-six per cent. of patients had neurosyphilis and 18.5 per cent. had latent syphilis with positive Wassermann reactions. Duration of infection ranged from four months to twenty-six years, more than half being in the second decade of their infection. Ages ranged from 8 to 59 years. The matter of hepatic involvement is important because of its bearing on the cause of the jaundice. Only 9 per cent. of the patients had palpable livers, and 4 per cent. had palpable spleens. Abdominal tenderness on first examination was present in 16 per cent., about equally divided between the upper and the lower abdomen. In investigating for surgical causes of jaundice, it was found that only three patients gave a previous history of icterus, and one was jaundiced from hepatic cirrhosis at the time of entry. One patient had a medical diagnosis of probable cholecystitis before jaundice appeared, and one was operated on in 1910 and gallstones were found. The condition of three patients which was clinically diagnosed cholecystitis cleared up under arsphenamin treatment. The gallbladder of one of two patients operated on during the attack was found to be negative, the other had cholecystitis with fine adhesions around the gallbladder and enlarged regional lymph nodes. Seven had sustained appendectomies and one had symptoms suspicious of appenditicis. In all only 23 per cent. of our cases presented anything even suggestive of abdominal nonsyphilitic pathology, and in only 13 per cent. did the signs point toward the liver and the biliary tract.

Laboratory findings on first examination showed 61 per cent. of the patients to have weakly or strongly positive Wassermann reactions. The percentage was reduced one half by the treatment they received. The incidence of jaundice had no appreciable effect on the percentage of positive reactions after the patients had recovered.

Sixteen per cent. of the patients had abnormal urines, the degree of abnormality being usually slight. The large majority had normal blood findings.

Study of accessible foci of infection in fifty-eight patients showed that about two thirds had moderately septic teeth or tonsils, and foci in the genito-urinary tract were at times present, but no distinct relation between these findings and the incidence of jaundice seemed demonstrable. Five patients whose dental and tonsillar foci had been removed nevertheless developed jaundice.

Prodromal Period.—Data on time relations from forty-seven cases show the prodromal period in 65 per cent. to be two weeks or less. Seven patients had prodromal periods of three weeks, and five had thirty days.

Of special interest in the consideration of an etiologic infection was the frequency of coryza, tonsillitis and pharyngitis, influenza and grippe as a feature of the prodromal period. Forty-one per cent. of fifty-eight patients of whom data were obtained developed such manifestations before or in association with their jaundice. One patient had pneumonia with jaundice, and another had a sequence of coryza, bronchitis, influenza, jaundice, and bilateral otitis media, with recovery. The symptomatology of the prodromal period based on fifty-two cases is given in Table 1.

TABLE 1.—SYMPTOMATOLOGY

	Percentage of Patients
Lassitude and prostration	77
Loss of weight (up to 9 pounds)	45
Coryza, tonsillitis, pharyngitis, influenza, etc.	41
Pains in joints and muscles	40
Nausea and vomiting	32
Constipation	20
Anorexia	19
Diarrhea	13
Cutaneous manifestations (purpura, erythema)	4

Aching pains and stiffness in the back, shoulders and legs were much complained of, and were at times so severe that patients could not rise from bed in the morning or raise their arms high enough to dress their hair. Minor symptoms complained of included headache, dizziness, drowsiness and epistaxis. In some cases the prodromal period was so short as scarcely to deserve the name.

Symptoms at the Height of the Attack.—The symptoms at the height of the attack were essentially those of the prodromal period, continued with gradually decreasing severity through the early days of the icterus. This was especially true of the gastro-intestinal phase. Two patients, however, noticed actual and surprising relief of symptoms when the jaundice appeared. The disappearance of the jaundice was slow, the average duration in all cases treated and untreated being thirty-seven days. Fever was seldom observed and was prominent only in three cases. No reliable information was available of patients reached by questionnaires. Jaundice varied from a slight tinge to the most intense icterus. Unfortunately, data on the condition of the liver were recorded in only twenty-seven cases, of which 47 per cent. showed definite diffuse enlargement ranging from a palpable edge at the costal margin to an edge 10 cm. below the ribs. Bulging of the anterior surface was noted once. Fifteen of the sixteen patients

with hepatic enlargement had not had palpable livers on first examination, and in only two, the one with hepatic cirrhosis, did the liver remain palpable after the attack passed off. In general, the liver was not examined until after jaundice appeared. Abdominal tenderness, equally distributed between the upper and lower right quadrants and the epigastrium, was definitely present in 39 per cent. of fifty-four cases examined.

The Laboratory Findings.—The stool varied in color from white and waxy in one case, through gray and clay color in the majority of cases, to normal in three cases. Two stools tested for bile showed its presence. Thirty-five and one half per cent. of forty-one cases examined showed evidence of renal irritation, usually in the form of hyaline casts. Bile was usually, though not invariably, present.

Blood urea estimations and renal functional tests were made on seven patients with normal results in five. In the most interesting abnormal case the patient developed very severe vomiting and stupor suggesting uremia during the early days of the attack. He presented successively 40 mg., 87 mg., 30 mg. and 40 mg. in a period of twenty-eight days, the highest reading representing the height of the attack. This patient was a tabetic whose phenolsulphonephthalein return (intramuscular) had been 55 per cent. In the later cases of the series and particularly in one which threatened a serious outcome an effort was made by Dr. Willis L. Lemon to interpret the nature of the condition in terms of the findings in the duodenal contents.

INTERPRETATION OF THE DUODENAL FINDINGS

From Table 2 it will be apparent that the jaundice was in part hematogenous. In one patient who was critically ill the readings were high during the severity of his illness, but returned to normal on his recovery, denoting that the cell destruction is not persistent. The hemolysis, as evidenced by the total number of units and particularly the units of urobilinogen, was in direct proportion to the severity of the illness of the patient. Two patients who were only indisposed had normal readings. The degree of anemia bore the same relationship to the severity of the illness as did the hemolysis. The presence of acholic stools and of bile in the urine gave evidence that the jaundice was obstructive in type as well as hematogenous. The fragility of the cells was undisturbed or slightly increased, as might be expected in patients who had received an arsenical preparation. The cholesterol readings were insufficient in number and inconclusive.

With reference to the coincidence of jaundice with influenza, it has been my (Lemon) experience, based on the observation of cases of influenza and pneumonia seen in the Clinic, that jaundice is a

TABLE 2.—Analysis of Laboratory Findings in Eight Patients With Jaundice

No.	General Health	Duration	Liver	Stool	Urine	Blood Count	Fragility	Cholesterol	Bile Pigments	Bile Pigments After Recovery
288222	Extremely sick patient; emaciated; painless jaundice	5 weeks	Large and tender	Positive for bile	Urobilin but no bile or urobilinogen	Hb. .....60% R.B.C. ...4.25 W.B.C. 22,700 No. ..200 cells P. .....78.5% S.L. ....13.0% L.L. .... 5.5% E. ..... 0.5% B. ..... 1.5% N.M. ... 1.0%	Control 0.40-0.32% Patient 0.40-0.30%	Bloor I...103 mg. Bloor II..146 mg. Difference 43 mg. Normal Bloor I Slight increase, no difference (Luden)	Duodenal contents: normal yellow Urobilinogen.... 7 × 200 = 1,140 Urobilin.....10 × 200 = 2,000 Total No. units..... 3,400	Duodenal contents: Urobilinogen..... 0 Urobilin 2 × 200 = 400 Total No. units...400
136432	Recovering from painless jaundice	4 weeks	Slightly tender	Acholic	Bile, urobilin and urobilinogen	.....	.....	.....	Duodenal contents: Urobilinogen.... 5 × 200 = 1,000 Urobilin..... 4 × 200 = 800 Total No. units..... 1,800	
298157	Recovering from painless jaundice; lost 14 lbs. in two weeks	3 weeks	.....	Positive for urobilin	Bile	Hb. .....78% R.B.C. ....4.7 W.B.C. 5,460	.....	.....	Duodenal contents: Urobilinogen.... 4 × 200 = 800 Urobilin.....27 × 200 = 5,400 Total No. units..... 6,200	
296460	Recovering from painless jaundice, mild type	10 days	Palpable but not tender	Acholic	Moderate amount of bile	Hb. .....54% R.B.C. ...4.81 Normal differential	Control 0.42-0.36% Patient 0.40-0.28% increased fragility	.....	Duodenal contents: normal yellow Urobilinogen.... 3 × 200 = 600 Urobilin.....11 × 200 = 2,200 Total No. units..... 2,800	
296287	Recovering from painless jaundice	1 week	Tender on pressure	Putty colored; acholic	Bile, urobilin and urobilinogen	Hb. .....78% R.B.C. ....4.8 W.B.C. 7,200 Normal differential	Control 0.42-0.36% Patient 0.36-0.28% increased resistance	Bloor I... 77 mg. Bloor II..145 mg. Normal Bloor I but high difference possibly due to present treatment (Luden)	Duodenal contents: Failure due to light Urobilinogen..... 0 Urobilin..... 1,400 Total No. units..... 1,400	
288259	Recovering from painless jaundice	.....	.....	.....	.....	.....	.....	.....	Duodenal contents: Urobilinogen.... 2 × 200 = 400 Urobilin..... 4 × 200 = 800 Total No. units..... 1,200 Normal but on upper limit and border line in character	
79724	Able to be at work; jaundice almost disappeared; no treatment for two months	.....	.....	.....	.....	.....	.....	.....	Duodenal contents: normal yellow Urobilinogen.... 1 × 200 = 200 Urobilin..... 3 × 200 = 600 Total No. units..... 800	
314088	Recovering from painless jaundice; sclera still discolored; streptococci found in submaxillary gland secretion	3 weeks	.....	Positive for bile	Bile; urobilin faint trace; urobilinogen absent	Hb. .....77% R.B.C. ...4.78 W.B.C. 8,600	.....	.....	Duodenal contents: fluid, normal yellow Urobilinogen..... 0 Urobilin..... 3 × 200 = 600 Total No. units..... 600	
287857	Slight indisposition	1 day influenza 3 weeks before	Not enlarged or tender	Normal	Bile	Hb. .....75% R.B.C. ...4.66 W.B.C. 5,800	0.36-0.28% incomplete, increased resistance	.....	Duodenal contents: Urobilinogen..... 0 Urobilin..... 3 × 200 = 600 Total No. units..... 600	

relatively unusual complication. The large majority of these cases, however, were not followed up, or were not under observation for any great length of time, so that they do not form satisfactory material for comparison with the material of the present report, nor was the total number of influenza cases observed as large as the series of patients observed in the Section on Dermatology and Syphilology.

Complete recovery without sequels and with a gain in weight was the rule in 90 per cent. of patients. Of those who fell short of recovery one had a diffuse nephritis, one an anemia, one became dyspneic (cause not known), and two who had had apparently normal hearts on first examination, developed respectively peri-aortitis and mitral endocarditis. Nine per cent. suffered recurrences of jaundice. Of these two died, one of actinomycosis and the other of an unknown cause; a third relapsed while receiving bladder irrigations for cystitis. A fourth, who suffered a slight recurrence at the end of a course of treatment, was found to have apparently a chronic duodenitis.

Treatment of the Jaundiced Patients.—Antisyphilitic treatment was discontinued temporarily in 66 per cent. of patients. In those in whom it was continued it seemed to exert no marked influence. At the suggestion of Dr. W. H. Goeckermann patients were given tablets of ox-gall, pancreatin, and sodium bicarbonate, the only form of ox-gall available at the time, in an effort to apply the observations of Eppinger on the effect of this substance in diminishing the viscosity of the bile in cholangitis. In twenty-four cases thus treated, with the addition of sodium phosphate, the average duration from the beginning of jaundice was thirty days. In thirty-eight cases in which sodium phosphate alone was given, with general dietetic measures, the average duration was forty-five days. We do not pretend that such an observation constitutes a final demonstration of the utility of this treatment.

Etiology of the Jaundice; Surgical Conditions and Syphilis.—That surgical conditions of the biliary tract played an insignificant part in our series is apparent from the foregoing description of the material. Syphilis was, of course, directly responsible for the condition of a patient who was jaundiced at first examination. Syphilis, if instrumental in producing the jaundice of the remaining cases, would have to take the form of precocious icterus, which is eliminated in all but two cases by the stage of the disease, or occur as a hepatorecidive in an inadequately treated case, or as a Herxheimer response in a liver already involved before treatment was begun. Practically all of our patients had already received an amount of treatment before jaundice appeared which should exclude the possibility of a hepatorecurrence and should likewise render extremely remote the possibility of a Herxheimer flare-up in the affected organ in an otherwise obscure

hepatic involvement. The most forcible argument against a syphilitic etiology, however, consists in the fact that two thirds of the patients recovered during a suspension of antisyphilitic treatment, and not under treatment, and that 23 per cent. of them were, in fact, never treated for syphilis again after their jaundice appeared. Four of our patients with jaundice did not have syphilis. The instrumentality of syphilis in the production of the jaundice observed by us must, therefore, be regarded as all but negligible.

The Relation of Arsphenamin to Jaundice.—The literature of this question accepts tacitly as a test of such a relation the presence of evidences of arsenical poisoning, especially finding the metal in the urine and liver. If this test fails, the claim for arsphenamin etiology loses much of its force. We concede our study to be incomplete in that no such determinations were made for our cases. According to the recent literature arsenic has been conspiciously absent in the urine and in the liver at necropsy. The demonstration of an arsphenamin etiology, however, seems to require further that there shall be some fairly constant relation between the time of administration of the drug, the amount administered, and the onset and severity of the jaundice. Moreover, the administration of arsphenamin to a patient suffering from arsphenamin icterus, should aggravate the condition and lead to serious consequences, or lead fairly constantly to relapse if the patient were recovering.

Jaundice developed in our patients at all periods of time from the day after injection to forty weeks after the last dose of arsphenamin. Table 2 indicates the evenness with which the onset was distributed over a long period and the lack of any distinctive time relation. So irregular a distribution of onset seems to us opposed to the conception of a purely arsphenamin etiology.

The widest differences were apparent in the amount of arsphenamin received by patients who developed jaundice, and equally striking discrepancies occurred between the severity of the jaundice and the amount of the drug administered. Eight of our patients had had from five to twenty-five arsphenamin injections, without developing jaundice, before their treatment was begun in our department. Two patients developed a very severe jaundice after they had received as little as 0.7 gm. On the other hand, a very mild jaundice developed in two patients who had received 5.5 and 6.8 gm., respectively. Seventy per cent. of the patients who developed jaundice had had amounts ranging from 2.2 to 2.7 gm., representing a single course of six injections, covering a period of six weeks. Approximately one fourth of the patients had mild attacks, one half had moderate, and one fourth severe attacks. Twelve per cent. of the cases of jaundice

developed in patients who had received less than 2 gm., and 17 per cent. developed in patients who had received in excess of 5.7 gm. We think it probable that the preponderance of first-course patients (those who received 2.7 gm.) is at least in part explainable by the fact that such patients are much more easily persuaded to keep in touch with the service for observation than are second and third course patients. The usual interim home period in our plan of treatment is four months, which would make it appear that patients who were given their first course of treatment in the summer and early fall developed jaundice in the late fall and in the winter.

TABLE 3.—DISTRIBUTION OF ONSET IN RELATION TO ARSPHENAMIN ADMINISTRATION

Time of Onset	Percentage of Patients
While receiving the drug	14
Within from 1 to 4 weeks after receiving the drug	14
Within from 5 to 6 weeks after receiving the drug	0
Within from 7 to 10 weeks after receiving the drug	20
Within from 11 to 14 weeks after receiving the drug	28
Within from 15 to 18 weeks after receiving the drug	8
Within from 19 to 23 weeks after receiving the drug	14
After 23 weeks	2

Fifty per cent. of our patients resumed arsphenamin treatment immediately on their recovery from jaundice, receiving the drug in amounts as large as those used before the attack, without apparent ill effects. Sixteen per cent. of our patients continued their arsphenamin treatment throughout their jaundice, or resumed it while still jaundiced, without apparent ill effect. These two facts in particular seem to us fairly good evidence that the arsphenamin was not the sole or even the principal causative factor in our group.

Relation of Mercury to Jaundice.—Arguments similar to those for arsphenamin apply to the question of the relation of mercury to the jaundice in our series of cases, and facts not unlike those discussed for arsphenamin were elicited. Five of our patients had received no mercury, and one of them had had none for two years and three months. Three had received insignificant amounts ranging from two to five inunctions. Two received inunctions while they were jaundiced without ill effect, two took pills, and one received the bichlorid intravenously twice a week without effect on the jaundice. One third of our patients were taking inunctions at the time their jaundice developed, but this is more easily explainable as a coincidence than as a consequence, since inunctions form the constant interim treatment of the department and a large proportion of the patients were away on home treatment when their jaundice appeared. No quantitative relation between the amount of mercury received by a given patient and the

incidence of jaundice was apparent. Certain patients who became jaundiced had received as high as 185 four-gram inunctions. Others had barely completed their second inunctions. We believe that these observations effectually exclude mercury from the rôle of exciting cause.

Evidence for an Infectious Exciting Cause.—The examination of our group of cases for indications of an infectious etiology disclosed

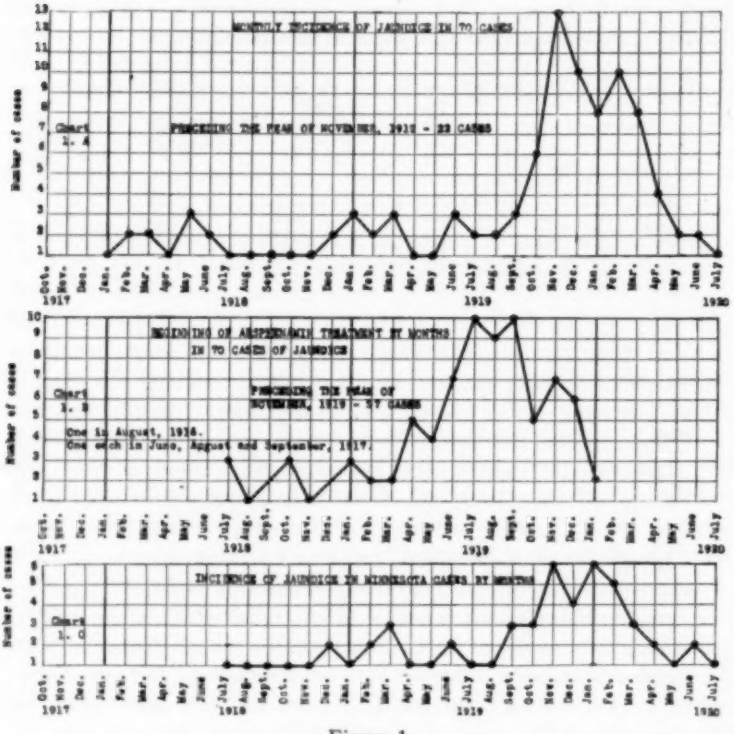
MONTHLY INCIDENCE OF JAUNDICE IN 70 CASES
PEAKING THE PEAK OF NOVEMBER, 1919 - 22 CASES
Chart 1. A
Number of cases
BEGINNING OF ANTIPHILIC TREATMENT BY MONTHS IN 70 CASES OF JAUNDICE
PEAKING THE PEAK OF NOVEMBER, 1919 - 22 CASES
Chart 1. B
One in August, 1916.
One each in June, August and September, 1917.
INCIDENCE OF JAUNDICE IN MINNESOTA CASES BY MONTHS
Chart 1. C
1917
1918
1919
1920

Figure 1

a variety of circumstantial evidence. The overwhelming proportion of the jaundice occurred between October, 1919, and April, 1920, with peaks in November and February. This period was one of widespread systemic and respiratory infection, and included the second wave of epidemic influenza. It is interesting that little or no jaundice occurred with the epidemic of 1918, which would make jaundice, if there is any connection with influenza, comparable in a way to lethargic encephalitis as perhaps a sequel, associate, or modification rather than

a direct complication. The plotted curve of monthly incidence of jaundice in twenty-nine cases occurring in the state of Minnesota shows the same distribution, in point of time, as the larger series. The second peak in February is identical with the peak of the epidemic influenza wave of the present year (1920).

Chart 1 B, in which is plotted the month in which arsphenamin treatment was begun, when compared with Chart 1 A shows that while 80 per cent. of our patients had received arsphenamin prior to the maximum incidence of jaundice in November, 1919, only 31.5 per cent. had developed jaundice up to that time. It seems probable, therefore, that the remaining 52 per cent. of patients were precipitated into jaundice by some agent that became operative between November, 1919, and March, 1920. The only other way to explain the acuteness of the rise of the jaundice curve is to consider the possibility of a technical error or a peculiarity of the drug administered. Both possibilities seem to us unlikely on account of the constancy of the technic, the reliability of the product, and the diminishing incidence of other forms of reaction throughout the entire period from January, 1917. The peak of the arsphenamin curve from July to September, 1919, is, we believe, to be explained as incidental to our four months' interim treatment system and the greater ease with which first-course patients as compared with the second and third course patients can be kept under observation and returned.

Further circumstantial evidence for an infectious exciting cause is compiled in Tables 4 and 5.

TABLE 4.—Epidemiologic Relations

	Percentage of Patients
"Colds" and influenza prevalent in vicinity	59
Influenza epidemic (mild) in vicinity	44
Onset of jaundice with nose, throat and respiratory symptoms	41
Jaundice appeared in same town at same time	25
Evidence of direct exposure of patient to jaundice	22
Replies from physicians confirm epidemiologic associations	4 of 6
Total presenting one or another evidence of an infectious character or of association with influenza	73

TABLE 5.—Possible Direct Contacts

	Cases
Jaundice in same household (husband, brother, boarder)	3
Friends and associates jaundiced	4
Jaundice among neighbors	5
Physician and patient jaundiced at same time	1

The replies of physicians, while few in number, deserve more than passing mention. Dr. J. J. Catlin of Buffalo, Minn., stated that he had observed three distinct epidemics of jaundice during the past

fifteen years. The latest one had developed during the late summer and fall of 1919. The symptoms in most cases included coryza, pharyngitis, cough, malaise, fever, vomiting before the appearance of jaundice, pains throughout the body, loss of weight and a light-colored stool. He further remarked, "Some of these cases have been very mild. I have seen families with three cases at a time. There were usually quite pronounced gastro-intestinal symptoms. Occasionally there were families where one or more were jaundiced and another would have the same symptoms and no jaundice." A communication from Dr. George Walker of Roundup, Mont., stated that he had observed three instances of jaundice associated with influenza in about 100 cases but had not observed anything approaching an epidemic. The symptoms associated with the cases of jaundice observed by him included pharyngitis, malaise, fever, vomiting before and after the jaundice appeared, myalgia, loss of weight, clay-colored stools and tenderness over the liver. A communication from Dr. R. B. McBride of Dallas, Texas, stated that he had observed about twice as many cases of jaundice as usual during the past year, but nothing approaching an epidemic. He has noted jaundice following an epidemic of colds. The liver in his cases has usually been palpable and slightly tender. Dr. H. L. Crane of Lead, S. D., in writing with regard to one of our jaundiced patients who was under his care, stated, "I am now of the opinion that his trouble was due to this epidemic form of cholangitis that has been present here for several months. Two of the six reports received from physicians were frankly negative.

SUMMARIES OF CASE REPORTS

The following summaries of cases illustrate a number of suggestive minor circumstances:

CASE 1 (300829).—Following the third arsphenamin injection of the first course, the patient caught cold, developed bronchitis and influenza, then jaundice and double otitis media. Immediately on recovery arsphenamin was resumed; three more injections as large as the first were given without event.

CASE 2 (297229).—The patient developed jaundice twelve weeks after a course of six neo-arsphenamin injections (total 2.4 gm.). The attack lasted three weeks. The patient's wife while nursing him acquired influenza. He has since received a second course of neoarsphenamin, larger dosage than the first, without event.

CASE 3 (287428).—The patient developed jaundice twenty-three weeks after a single course of 2.3 gm. arsenobenzol (six injections). The attack was preceded by a prolonged severe cold. The patient's husband, who had not had antisyphilitic treatment but had accompanied his wife to Rochester, became jaundiced three weeks after the onset of her attack (a frequent incubation period).

CASE 4 (298430).—This patient received six injections of arsphenamin in January, 1920, three months after a patient (Case 3 [287428]) who was a friend of hers, received a similar course. After the second patient returned home, she called on the first patient and found her recovering from jaundice. The sec-

ond patient developed jaundice shortly after, the exact time not being known. This patient states that during this time a number of employees at her husband's office were jaundiced. Both of the patients (Case 3 [287428] and Case 4 [298430]) have since received full courses of arsphenamin treatment without complications.

Case 5 (270549).—The patient's jaundice began seventeen weeks after the last arsphenamin injection of the first course. This patient, who lived in a small town, went to a neighboring city of 43,000 and was told by his doctor that there were many cases of jaundice and some of sleeping sickness in town. No reply was received from a questionnaire sent to the physician. The onset of this patient's attack consisted of jaundice followed on the second day by signs of a cold and rheumatism in the knees and elbows, and later in the shoulders.

Case 6 (296919).—This patient had a latent neurosyphilis, with a negative serum Wassermann reaction. No previous treatment had been given. A "tubing reaction" followed the second arsphenamin injection of the first course. The patient was nauseated for one week and then became jaundiced. Her course of treatment was continued with slightly reduced dosage and without ill effect. The liver was not palpable.

Case 7 (278387).—The patient received three injections of 0.3, 0.4 and 0.3 gm. arsenobenzol and became mildly jaundiced. Jaundice became markedly worse after a spinal puncture and still worse following 0.3 gm. of neo-arsphenamin. Two more injections of 0.4 gm. neo-arsphenamin at the usual weekly intervals were without injurious effect, and the patient began to clear up at the time of her departure from the Clinic. It is possible that the exacerbation following the third injection (neo-arsphenamin) was due to the drug, but since a fourth and fifth larger injections were without effect and a similar exacerbation followed spinal puncture, it seems unlikely that the arsphenamin was responsible.

Case 8 (177361). (Not included in this series).—The chief operating room nurse of the Section of Dermatology and Syphilology, through whose hands every jaundiced patient seen in the department had passed, after one week of malaise developed a toxic erythema of the face, followed by severe urticaria, which lasted three days. She complained for two more weeks of pain and stiffness in the back and shoulders, so severe that she could scarcely rise from bed or dress her hair. She then became slightly jaundiced, with bile in the urine. The liver was not palpable. At no time had she received any form of antisyphilitic treatment, nor had there been anything to suggest gallbladder pathology. A severe pharyngitis developed during the jaundice.

A case illustrative of the fairly sharp distinction that we believe can be drawn between jaundice of late syphilitic origin (hepatic cirrhosis) and the type of acute hepatitis with jaundice discussed in this paper, is the following:

Case 9 (272613).—A patient with syphilitic cirrhosis of the liver, accompanied by moderate jaundice and with aneurysm of the descending aorta, had nocturnal attacks of substernal pain of great severity. Under mercury by inunction, with neo-arsphenamin injections and massive doses of iodids, he made a striking improvement. His jaundice disappeared, his liver shrank from 15 cm. to 5 cm. below the costal margin, and his aneurysmal pains disappeared. Seven months later (Jan. 21, 1920) after interim mixed treatment by mouth he returned to the hospital in excellent condition for further treatment with inunctions and iodids. Influenza was epidemic in Rochester at this time, a fact which occasioned the patient some uneasiness (this month was also that of the second peak of the jaundice curve). February 3 he complained of rather severe epigastric pain, and was dizzy and nauseated. *There was no*

localized abdominal tenderness. Two days later the gastro-intestinal symptoms still persisted, and he became slightly jaundiced. The jaundice increased to a moderate degree. February 8 there was still considerable epigastric pain and a severe aching pain in the back. Tenderness was now present over the right subcostal region. The liver was markedly enlarged over its usual size and jaundice continued moderate. February 11 the jaundice was clearing rapidly and by February 14 was practically gone, together with his other symptoms, *with the exception of a troublesome cough* that had developed during the attack. A slight loss of weight was apparent, but recovery was otherwise complete. At no time was the patient febrile. During the jaundice, inunctions had been discontinued, and no other antisyphilitic treatment was given. Inunctions were resumed when the jaundice disappeared and ten more had no effect in producing relapse.

Comment: Since no arsphenamin was administered and mercury was resumed without ill effect, it seems unlikely that these drugs were responsible. Since the patient had had considerable treatment previously, and recovered from his jaundice while treatment was suspended, a hepatorecurrence does not form a satisfactory explanation. The most probable explanation seems to involve an infectious element, suggested by the systemic symptoms and cough.

Bacteriologic Studies.—Our efforts to identify an infecting organism in these cases were disappointing. Cultures and animal inoculations made from the secretions of the nose and throat in seven early cases yielded only the usual organisms, and no evidence of hepatic involvement appeared in rabbits inoculated with them. A pure culture of *Bacillus mucosus* obtained from Case 8 (177361) produced death in a rabbit with multiple hemorrhage into the muscles. Blood culture from one patient was negative. We believe, in retrospect, that systemic blood culture during the prodromal period deserves further trial. A stool, in a typical case, yielded only the colon bacillus. In view of the findings reported in the literature investigation for paratyphoid organisms should be carried out.

The paucity of our bacteriologic findings, incomplete though our investigations were, accords with the findings in the literature and suggests too the possibility that the invading organism may be one of the familiar quasi-saprophytic types which in normal persons or in times when epidemic infections such as influenza are not prevalent, with their consequent reduction in the general level of resistance of the population, are unable to overcome the resistance of their hosts.

Discussion of the Literature.—Our survey of the literature was intentionally postponed until our impressions had taken form from the evidence at hand. There appears to be much in recent publications to confirm our impression of the existence of an epidemic catarrhal jaundice of nonspirochetal origin. Curiously enough practically no reference to this literature and no consideration of the possibility that this epidemic jaundice may be masquerading as an arsenical complication of antisyphilitic treatment appears in the recent French and

American literature. A vigorous discussion between Milian [1] as a proponent of syphilologic etiology, and Sicard and his collaborators [2] as proponents of arsenical etiology, has found expression in articles during October and November, 1919, in the *Bulletin de la Societé médicale des Hôpitaux de Paris*. Other isolated reports, such as those of Eschbach,[3] have enlarged the supposed field of toxic factors to include mercury. Conspicuous in the American literature have been the articles of Scott and Pearson,[4] Lynch and Hoge,[5] and Bailey and Mackay.[6] Strathy, Smith and Hanna [7] in the British literature have also discussed delayed arsenical poisoning on the basis of fifty-eight cases following arsphenamin administration. Sicard argues, as have we, that the amount of treatment received by many of the patients under his observation precludes the possibility of hepatorecidives and Herxheimer phenomena as the cause of their jaundice. Treatment in some of his cases frequently included as high as 10 gm. neoarsphenamin. Milian, on the other hand, points out, with equal justice, that if arsphenamin treatment is continued throughout the period of jaundice the patient will recover. He argues that this constitutes a therapeutic test and demonstrates beyond question the syphilitic character of jaundice. We again find ourselves in accord with Milian's observations but not with his conclusions, since a number of our patients recovered under the continuation of treatment for syphilis. The partial character of the views expressed seems to be due to the small number of cases observed by each author, which affords little opportunity to appreciate the variety of possibilities involved.

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1. Milian, G.: Trois cas d'ictère au cours du traitement a l'arsenobenzol, leur nature syphilitique, Bull. et mém. Soc. méd. d. hôp. d. Par. **43**:821, 1919.

2. Sicard, Haguenau, and Kudelski: L'ictère tardif post-novarsenical et le traitement novarsenical par petites doses repetées, Bull. et mém. Soc. méd. d. hôp. de Par. **43**:880, 1919; Traitement de la syphilis nerveuse chronique. Les éléments de controle de la médication novarsenicale, Bull. et mém. Soc. méd. d. hôp. de Par. **43**:833, 1919.

3. Eschbach, M. H.: Contribution au rôle du novarsénobenzol dans les ictéres chez les syphilitiques et dans les dyscrasies sanguines, Bull. et mém. Soc. méd. d. hôp. d. Par. **43**:1120, 1919.

4. Scott, G. O., and Pearson, G. H. J.: A Preliminary Report on Syphilitic and Arsenical Jaundice, Am. J. Syphilis **3**:628, 1919.

5. Lynch, T. J., and Hoge, S. F.: Toxic Jaundice Following "Intensive" Antisyphilitic Treatment, J. A. M. A. **73**:1687 (Nov. 29) 1919.

6. Bailey, C. V., and MacKay, A.: Toxic Jaundice in Patients Under Antisyphilitic Treatment: A Study of the Chemical Analyses of the Blood and Urine, and Observations on the Effect of Exercise and Diet in the Treatment of Syphilis, Arch. Int. Med. **25**:628 (June) 1920.

7. Strathy, G. S., Smith, C. H. V., and Hannah, B.: Delayed Arsenical Poisoning: A Report of Fifty-Eight Cases Following the Administration of "606" Preparations, Journal-Lancet **1**:802, 1920. Also: Canad. M. A. J. **10**:336, 1920.

Lynch and Hoge [8] reported three cases of jaundice occurring recently during treatment for syphilis, one of which came to necropsy. These authors frankly concede that no traces of arsenic could be found in the liver of the patient coming to necropsy or in the urines of any of the three. Notwithstanding this negative finding they attribute a hepatitis, amounting in their fatal case to almost complete destruction of the liver parenchyma, to antisyphilitic treatment. That the therapy which they described as intensive is by no means the most intensive technic employed was subsequently pointed out by Pollitzer.[8] It may not be out of place at this point to call attention to the fact that the prodromal symptoms in their Cases 2 and 3 were very similar to the typical picture in our series. The jaundice in Case 2 did not appear until thirteen weeks after the course of treatment. Their survey of the literature naturally did not include a number of articles which have become available since the publication of their findings. They note, however, that Fenwick, Sweet and Lowe [9] were likewise unable to demonstrate arsenic in the urines of patients whom they reported as dying of icterus gravis following the injection of neoarsphenamin. The possibility of an infectious epidemic factor in the jaundice is apparently not considered by Lynch and Hoge.

Scott and Pearson [4] in their consideration of syphilitic and arsenical jaundice direct attention to the conventional types of early and late syphilitic and arsenical jaundice already recognized. They do not, however, mention the possibility of an incidental intercurrent infectious jaundice nor do they interpret their findings in the light of this possibility. They apparently accept the view that jaundice occurring during treatment for syphilis must be due to syphilis or arsenic.

In a series of forty cases very carefully studied by Bailey and Mackay with particular reference to the laboratory findings, these authors likewise note the entire absence of arsenic in the urine of all patients examined, at periods ranging from 25 to 157 days after the last arsphenamin administration. They apparently attribute the jaundice to antisyphilitic treatment and suggest as an explanation of the delayed effect the possibility that each dose inflicts a certain amount of injury to the liver, the ultimate acute explosion being induced by the removal of dietetic and physical restrictions when the period of treatment is ended. These authors also apparently do not consider the possibility that an acute infection may serve as an exciting cause of reaction on the part of a therapeutically damaged liver. Their series of cases includes a case of probable syphilitic hepatitis (Case

8. Pollitzer, S.: "Intensive" Antisyphilitic Treatment, J. A. M. A. **73**:1852 (Dec. 13) 1919.

9. Fenwick, P. C., Sweet, G. B., and Lowe, E. C.: Two Fatal Cases of Icterus Gravis Following Injections of Novarsenobillon, Brit. M. J. **1**:448, 1918.

1) and a case of jaundice (Case 24) without evidence of syphilis or treatment for it. A number of their patients apparently developed exfoliative dermatitis in association with the jaundice, which in our opinion certainly strengthens the view that the jaundice was of arsenical origin. On the other hand we have been impressed with the fact that exfoliative accidents in the course of arsphenamin administration can be precipitated by acute infections such as tonsillitis. Three of our patients had eruptive manifestations and a fourth, with neither syphilis nor treatment for it, had a prodromal erythema and urticaria. Michelson [10] has likewise mentioned the coincidence of streptococcal septicemia and exfoliative dermatitis in a patient under treatment for syphilis.

Evidence pointing to the existence of a nonspirochetal epidemic form of jaundice has likewise been accumulating in the literature of the past year. In December, 1919, Guiteras [11] reported an epidemic of febrile jaundice, at first confused with yellow fever, occurring in the island of Barbados in 1919. This jaundice was associated with albuminuria. Guiteras, in summing up the literature, says that epidemic febrile and infectious jaundice has been more prevalent all over the world in recent years than formerly. In Japan and Flanders the epidemic seems to have been spirochetal in origin, but in Egypt and the Gallipoli peninsula a paratyphoid infection seems to have been the probable cause.

Lindstedt,[12] in April, 1919, illustrates with a series of eight cases the symptomatology and incubation period of a nonspirochetal form of catarrhal jaundice with examples of its probable transmission from patient to patient. The incubation period in his cases varied from two to four weeks but he believes it may be longer. The similarity of this observation to our own data on the prodromal period is evident. Lindstedt believes the entity to be clinically, bacteriologically and epidemiologically distinct from Weil's disease.

In May, 1919, Willcox [13] in his third Lettsomian lecture discusses recent experience with epidemic catarrhal jaundice. He points out that a mild and a grave form are recognizable and that in Mesopotamia and the Dardanelles the jaundice curve attained its maximum about three weeks after dysentery. The epidemic character appeared to be due to a common cause rather than to spread from person to person. This same observation seems somewhat applicable to our

10. Michelson, H.: Discussion, J. A. M. A. **73**:905 (Sept. 20) 1919.

11. Guiteras, J.: Epidemic of Febrile Jaundice in Barbados in 1919, New Orleans M. & S. J. **72**:360, 1919.

12. Lindstedt, F.: Zur Kenntnis des Icterus catarrhalis und dessen Inkubationszeit, Deutsch. med. Wchnschr. **45**:434, 1919.

13. Willcox, W. H.: Epidemic Catarrhal Jaundice, Lancet, **1**:930, 1919.

cases. A paratyphoid organism was identified by Sarailhé and Clunet.[14] No evidence of a spirochetal origin could be found in spite of much effort. Willcox believes that epidemic catarrhal jaundice is probably due to an intestinal infection causing duodenitis and a catarrh of the bile duct. He believes it to be associated with a transient bacteremia of which the causal organism is yet to be proved. These suggestions impress us as very much to the point.

In July, 1919, Tooth and Pringle[15] reported an epidemic of catarrhal jaundice occurring among British troops in Italy involving in all 111 cases. Two types were recognized, one with pyrexia and the other without. The seasonal incidence was overwhelmingly during September and October, 1918. In the milder cases the symptoms were usually pain in the epigastrium and indisposition, headache, nausea, vomiting, general malaise, and diarrhea. In the pyrexial cases, general pains, epistaxis and sore throat were noted and diarrhea was rare. In two cases inoculations of guinea-pigs for *Spirochaeta icterohemorrhagica* were positive but in a large number of other cases similar inoculations were negative. This leads the authors to believe that the pyrexial form of jaundice was probably due to spirochetal infection although they suggest the possibility of a relation to epidemic influenza, which was prevalent in Italy during these months.

In June, 1919, Bronson[16] reported the association of jaundice with influenza in children and at the same time Roussel and de Lavergne[17] reported five cases of jaundice associated with nephritis in a pneumococcal infection in which the organism was demonstrated in the blood. These cases occurred in January and March, 1919, during periods of recrudescence of an epidemic of "grippe." In September and October, 1919, Quenu, Küss and Brulé[18] called attention to the difficulty of recognizing cases such as the one they described, in which recurring attacks of fever with jaundice suggested angiocholitis except

14. Sarrailhé, A., and Clunet, J.: La "Jaunisse des camps" et l'épidémie de paratyphoide des Dardanelles, Bull. et mém. Soc. méd. d. hôp. d. Par. **40**:45, 1916.

15. Tooth, H. H., and Pringle, E. G.: Jaundice Among the British Troops in Northern Italy, Lancet **2**:144, 248, 1919; Supplementary Note on Jaundice Among the British troops in Northern Italy, Medico-psychological Association of Great Britain and Ireland: The annual meeting, Lancet **2**:248, 1919.

16. Bronson, E.: Catarrhal Jaundice Associated With Influenza in Children, Brit. J. Child. Dis. **16**:73, 1919.

17. Roussel, M., and Lavergne, M.: Cinq cas d'ictère par hepatonephrite, secondaire à une pneumococcie grippale. De la presence du pneumocoque dans le sang des ces malades, interpreté comme un signe de retention biliare dissociée, Bull. et mém. Soc. méd. hôp. de Par. **35**:587, 1919.

18. Quénu, E., Küss, G., and Brulé, M.: Septicémie à streptocoque non hémolitique accompagnée d'ictère et simulant une angiocholite lithiasique, Rev. de chir. **57**:785, 1919.

for the absence of gall stone colic pains, the streptococcus being found in the blood. In this connection it is interesting to recall certain of our own cases of recurrence.

The first discussion of acute epidemic jaundice which has come to our attention in recent American literature is that of Symmers.[19] During a period of ten weeks commencing in December, 1919, he stated that sixteen patients were admitted into Bellevue Hospital with severe jaundice, of whom 56.2 per cent. died. Symmers mentions moreover that he has observed a notable excess of cases of acute catarrhal jaundice during the past year. In eight of his cases search was made by various methods for a spirochetal organism but nothing could be found. In three of the patients who died with symptoms of acute yellow atrophy of the liver, chemical examination for heavy metals was negative. From Symmer's description we are inclined to believe that we have been dealing in most of the cases under our observation with an essentially similar process, though as a rule much less severe. He particularly notes the occurrence of lassitude, digestive disturbances, and signs indicative of bronchitis. Two of his patients were operated on under the impression that they were suffering from a surgical obstructive jaundice. Symmers points out in his study of the pathology that the destructive changes in the liver may so closely resemble acute yellow atrophy as to be indistinguishable in the gross. The type of jaundice discussed by Symmers was often hemorrhagic in character. In only one of our cases, however, was there a distinct purpuric eruption.

It will be apparent from the foregoing summary of the literature that an epidemic and possibly infectious form of catarrhal jaundice has been gradually coming to medical attention during the period in which we have been suspecting an infectious etiology for our cases. Attempts to identify a causative organism for this type of jaundice have not evidently thus far been entirely successful.

Due weight should be given to the possibility that without being the direct cause of hepatitis and jaundice, epidemic infections such as influenza, create widespread states of hypersusceptibility which result in the breakdown of tissues and organs subjected, as the liver is in antisyphilitic treatment, to therapeutic strains which are ordinarily borne without reaction. We have for several years past been impressed with the importance of this element in mercurial stomatitis, in renal reactions, and in the general course of syphilis, treated and untreated. Such a view would make infection a predisposing cause and arsphenamin and mercury the exciting cause of the jaundice we have observed.

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19. Symmers, D.: Epidemic Acute Hemorrhagic Jaundice of Toxic Origin, J. A. M. A. **74**:1153 (April 24) 1920.

The fact that the connection between arsphenamin, mercury, and the jaundice so often seems remote in time and quantitative relations, and that a further administration of these drugs so often is without injurious effect, makes this, in our estimation, a much less plausible theory than that of an infectious exciting cause.

We believe that the group of cases here presented serves to connect, in a measure, the general observations on epidemic catarrhal jaundice and observations such as those of Lynch and Hoge and other writers [20] who have sought to ascribe jaundice to the injurious effects of antisyphilitic treatment. Unquestionably, a certain amount of confusion has arisen in the literature from the fact that cases of undoubted syphilitic and arsenical jaundice, and of jaundice from surgical obstructive factors must occur in groups of patients under treatment for syphilis. So far as our own experience goes we believe that all the facts can be satisfactorily explained on the theory that a relatively small proportion are syphilitic and arsenical in origin, or have surgical conditions underlying them, but that the rôle of antisyphilitic treatment is usually only incidental and predisposing. The real cause of the great excess of cases of jaundice in our present experience as compared with our former seems to be, at least on the clinical evidence presented, the intervention of an extraneous, probably infectious, factor.

SUMMARY

1. Jaundice as a complication of the treatment of syphilis in the Section on Dermatology and Syphilology of the Mayo Clinic was a relatively rare occurrence during the period from August, 1916, to August, 1918. From August, 1918, to July, 1920, the incidence of this complication has increased over 1,000 per cent.

2. During the period from January, 1917, to July, 1920, there have been no notable changes in the technic of routine treatment of syphilis in this section, and one of the most reliable brands of arsphenamin and neo-arsphenamin has been consistently employed throughout the entire period, with a steady diminution of other types of complications. Neither have there been any conspicuous changes in the types of syphilis treated.

3. It is scarcely reasonable, therefore, to conclude a priori, that because most of the patients had syphilis and were treated for it, either syphilis or antisyphilitic treatment was responsible for the enormous increase in the incidence of jaundice among them. This

20. Eppinger, H.: Weitere Beiträge zur Pathogenese des Ikterus, Beitr. z. path. Anat. u. z. allg. Path. **33**:123, 1903; Ikterus, Argebn. d. inn. Med. u. Kinderh. **33**:107, 1908.

increase amounted to four times the maximum expectancy of jaundice as a complication according to the Meirowsky statistics. based on 225,780 injections.

4. A critical examination of the data obtained from the seventy cases occurring among our patients indicates that while several distinct types of jaundice are probably represented in the series, the large proportion were not ascribable directly if at all to the effects of syphilis, or of antisyphilitic treatment with either arsphenamin or mercury.

5. Syphilis as either a primary or a secondary etiology is largely excluded by the fact that the overwhelming proportion of the patients had had so much treatment before jaundice that Herxheimer effects and hepatorecurrences were practically eliminated.

6. Moreover, two-thirds of the patients recovered while antisyphilitic treatment was suspended, and one-fourth of those who recovered were in fact not again treated for the disease after the jaundice appeared. Four of the patients who were jaundiced did not have syphilis.

7. The argument against an arsphenamin etiology is based on the fact that no definite time sequence between the administration of arsphenamin and the incidence of jaundice can be detected, jaundice often appearing so late that any connection between the two occurrences is merely a matter for speculation. There was no constant relationship between the total dosage of arsphenamin administered and the severity of the hepatic symptoms which could not be largely explained on the basis of the time intervals in the interim home treatment system of the department. Arsphenamin had almost no unfavorable effect on those patients who continued it during their jaundice (16 per cent. of the series), and resumption of the arsphenamin in 50 per cent. of our patients as soon as their jaundice cleared up had no effect in producing relapse. Jaundice occurred in patients receiving neo-arsphenamin in isotonic solution, as well as in those receiving arsphenamin, so that a hemolytic influence of the drug seems not to be a factor.

8. Similar arguments applied in demonstrating the probable lack of relation between the adminstration of mercury and the incidence of jaundice lead to similar conclusions. Six of the jaundiced patients had never received mercury and several others had had insignificant amounts. Three received it throughout their jaundice without ill effect.

9. The study of this series of seventy cases discloses strong circumstantial evidence to the effect that an infectious agent, possibly associated with epidemic respiratory infections, is the exciting cause of the wave of jaundice observed since August, 1919.

10. The overwhelming proportion of the incidence of jaundice occurred between October, 1919, and April, 1920, with peaks in November and February. Prior to November, 1919, 80 per cent. of the seventy patients had received arsphenamin, but only 31.5 per cent. had developed jaundice. The remaining 52 per cent. not thus far jaundiced were, therefore, precipitated into the complication between November and April by some extraneous factor.

11. The months of maximum incidence of jaundice were those of epidemic respiratory and systemic infection, including influenza.

12. Forty-one per cent. of the patients of our series had coryza, tonsillitis, pharyngitis, influenza, "grippe," bronchitis, pneumonia or otitis media (named in order of frequency), intimately associated with the prodromal symptoms or actual appearance of the jaundice.

13. Symptoms suggestive of a systemic infection, with lassitude, arthritis and myalgia, backache, anorexia, nausea and vomiting, diarrhea or constipation, headache, dizziness, loss of weight, and nonlocalizable abdominal distress, usually preceded by several days or weeks, the onset of the jaundice and of hepatic symptoms as such.

14. The administration of ox-gall in tablet form seemed of some benefit in shortening the course of the jaundice in twenty-four of our cases.

15. Fifty-nine per cent. of our cases were associated with epidemics of colds and influenza in the vicinity.

16. One-fourth of the patients gave histories of jaundice developing in their localities, often in relatives, neighbors, and friends.

17. Four of six physicians testified to an association of jaundice with coryza, pharyngitis, and influenza in their recent experience. Two testified to epidemic features during the months included in our survey.

18. A total of 73 per cent. of our cases yielded one or another contributory evidence of a possible infectious factor in the etiology of the jaundice.

19. Incomplete bacteriologic studies of seven cases were unsuccessful in identifying a causative organism.

20. Study of the recent literature after our impressions were formed supplied confirmatory evidence that a form of nonspirochetal catarrhal jaundice of unknown etiology is coming into medical recognition, and has at various times and places in this country, Europe, and Asia, attained to epidemic proportions. This type of jaundice exhibits many of the salient features presented by the large proportion of our cases.

21. The possibility that this type of jaundice may be masquerading as syphilis or as an arsenical complication of antisyphilitic treatment

has been overlooked by recent writers on the subject, and undue aspersion, perhaps, has been cast on modern syphilotherapeutic methods. This is especially true since no arsenic could be found in the urines nor in the livers in necropsied cases. This apparently epidemic jaundice is associated with a hepatitis often closely simulating that produced by the heavy metals.

22. Laboratory studies and the literature suggest that the jaundice is, in part, hemotogenous and associated with gastro-intestinal lesions.

23. The intensity of the hemotogenous phase is proportional to the illness of the patient and is mild or absent in mild attacks.

24. The relation between influenza and the type of jaundice discussed is problematical. Little or no jaundice appeared among our patients during the influenza epidemic of 1918, and the time of incidence of the complication in 1919 and 1920 has been approximately but not exactly that of influenza. About 400 cases of influenza observed in the Clinic by one of us (Lemon) showed no special tendency to develop jaundice as a complication. It must be recalled, however, that the seventy cases here considered were collected from among a total of 5,200 patients. It is possible that the condition is a sequel or modification of epidemic influenza, rather than a direct complication.

25. We do not regard our contentions as proved conclusively. We believe, however, that while any agent potentially injurious to the parenchyma of the liver, such as arsphenamin, may, and probably does, act as a predisposing cause in the cases of hepatitis that have recently become so comparatively numerous in our experience, the exciting cause is probably an as yet unidentified infectious agent. This agent may be responsible for varying grades of hepatitis, ranging from mild cholangitis to extensive destruction of the affected organ, suggesting acute yellow atrophy.

OBSERVATIONS ON THE PATHOLOGIC PHYSIOLOGY OF CHRONIC PULMONARY EMPHYSEMA *

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The object of this paper is to record the results obtained from experiments on two patients with chronic pulmonary emphysema, of the so-called "large lunged" type. The work was undertaken in an effort to ascertain facts which might lead to a clearer appreciation of the disturbance in respiratory physiology in emphysema.

The gross and microscopic appearance of the lungs in this condition is well defined; also the impediment to the mechanics of respiration afforded by the loss of the elastic tissue of the lungs is appreciated. Further investigation, however, is necessary to show to what extent the degenerative process interferes with the aeration of the blood and the manner in which the body adapts itself to the altered conditions.

The work of Siebeck,[1] Porges, Leimdorfer and Markovivi,[2] Hoover [3] and others established the fact that the residual air and the functional dead space are increased, while the vital capacity is much diminished. Such changes naturally interfere with the alveolar ventilation and cause the patient with emphysema to suffer from a certain amount of pulmonary insufficiency particularly evident when a demand for increased gaseous exchange is to be met, as in exercise.

Another fact noted by most workers is the abnormally high tension of carbon dioxid maintained in the alveolar air. Different explanations have been offered for this. Recently, in experiments on dogs, Friedman and Jackson [4] found that there was an elevation in the carbon dioxid content of both the alveolar air and blood, when expiration was obstructed. This was attributed to the interference to the pulmonary circulation from the high intrabronchial pressure produced. Such elevations in intrabronchial pressure are not seen in patients with emphysema, except during an attack of asthma, or a paroxysm of coughing, when the impairment in the lesser circulation is probably an important factor in diminishing the gaseous exchange in the

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* First Hamilton Fiske Biggar Prize Essay of the Cleveland Medical Library Association.

1. Siebeck, R.: Deutsch. Arch. f. klin. Med. **102**:390, 1911.
2. Porges, O., Leimdorfer, A., and Markovici, E.: Ztschr. f. klin. Med. **77**:446, 1913.
3. Hoover, C. F.: Arch. Int. Med. **11**:52 (Jan.) 1913.
4. Friedman, E. D., and Jackson, H. C.: Arch. Int. Med. **19**:767 (June) 1917.

lungs. Other causes, therefore, must be considered in order to explain the high carbon dioxid content of the alveolar air in subjects with emphysema. These individuals may be comfortable and able to walk about tolerating in the alveolar air a percentage of carbon dioxid which would cause profound hyperpnea in a normal person. With no convincing evidence to the contrary it may be assumed that in such individuals the alveolar carbon dioxid is in equilibrium with the free carbon dioxid in the arterial blood. Recalling the well established physiologic relation between the activity of the respiratory center and the level of free carbon dioxid in the blood, it is at once apparent that the subject with emphysema represents a wide departure from the normal. For example, such patients have been observed to be perfectly comfortable when breathing from 8 to 10 liters of air per minute, with the alveolar carbon dioxid about 8 per cent.

After noting the unusual tolerance to carbon dioxid in several patients it was decided to study quantitatively the respiratory response to increasing percentages of carbon dioxid in the inspired air. The data thus obtained were compared to those found under similar experimental conditions in normal resting individuals. Two hospital patients with well marked chronic pulmonary emphysema were selected for this study. They were free of myocardial disease as far as could be determined clinically and with the aid of the electrocardiograph and at no time, since first observed, have any myocardial symptoms appeared. Particular attention has been paid to the circulation to eliminate as far as possible the effect of pulmonary stasis on the experimental results. The frequent association of myocardial disease with pulmonary emphysema has obviously limited the number of available subjects.

REPORT OF CASES

Case 1.—Eli B., male, aged 46 years, first came under observation in March, 1913, suffering from an attack of acute bronchitis. At that time he had definite pulmonary emphysema with a slight degree of cyanosis which persisted after recovery from bronchitis. He was not seen again until March, 1919, when he was admitted to the hospital complaining of cough and shortness of breath. The chest presented the typical "barrel-shaped" conformation with an increase in all diameters, particularly the anteroposterior diameter. There was narrowing of the subcostal angle during inspiration. The expiratory phase of respiration was prolonged and on auscultation numerous râles were heard throughout both lungs. No cardiac enlargement was demonstrable. The heart sounds were normal and there was no evidence of venous stasis, except during a paroxysm of coughing when the veins of the neck became very prominent. The blood pressure was 130 mm. systolic and 90 mm. diastolic. There was definite clubbing of the fingers. The cyanosis of the face and hands was quite marked for a few days after admission to the hospital but appreciably diminished as he recovered and was able to walk about comfortably, but even then the lips and finger nails presented a dusky, blue appearance. The patient had no fever at any time and the urine was normal.

Case 2.—Peter W., male, aged 49 years, has been in the hospital since first admitted in January, 1919. His complaint was shortness of breath and cough. Inspection showed the typical emphysematous thorax, with cyanosis of the face and hands. No pulmonary consolidations were found but a diffuse bronchitis was present throughout both lungs. The patient was apparently having much difficulty in ventilation, and expiration lasted about three times as long as inspiration. Marked narrowing of the subcostal angle occurred with inspiration. The blood pressure was 120 mm. systolic and 80 mm. diastolic. After ten days in bed the patient was much improved and has since been able to walk about fairly comfortably. A slight degree of cyanosis of the lips and mucous membranes of the mouth has persisted. Figure 1 shows the conformation of the thorax.

Fig. 1.—Patient Peter W., showing the conformation of the thorax.

RESPIRATORY RESPONSE TO CARBON DIOXID IN TWO NORMAL INDIVIDUALS COMPARED WITH TWO PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA

Description of Apparatus Used.—The subject is comfortably seated in a chair before which is a small adjustable table that may be readily placed on a level with the mouth. Projecting over the edge of this table is a rubber mouthpiece connected with a pair of gut valves. These valves [5] have been adopted in preference to others tried, because they are the most efficient and cause a minimum impediment to the

5. The technic of making the valves has been described by Pearce: Am. J. Physiol. **44**:369, 1917.

free ingress and egress of air. The subject inspires from a large 240 liter spirometer and expires into a smaller type of spirometer of 100 liters capacity. These spirometers are of the Tissot model, equipped with an eccentric wheel at the top so that the bell is counterpoised at all levels by means of a weight. Cylinders delivering carbon dioxid and oxygen through a Bohr meter into the inspiratory spirometer make it possible to prepare rapidly any desired concentration of the two gases for the subject to breathe. The bell of the inspiratory spirometer is so weighted that it tends to fall very slowly when opened to the air. Similarly the bell of the spirometer into which the subject expires is so balanced that it rises slowly when opened to the air, thus assisting the expiration. Attached to both spirometer bells is a small pointer which moves along a graduated scale at the side, showing the exact amount of air in the spirometers at any position of the bell. Non-collapsible rubber tubing connects the respiratory valves with the two spirometers. Both the tubing and the spirometer pipes are one inch inside diameter. On the intake pipe of the expiratory spirometer is a three way metal valve. By this arrangement the subject's expired air can be directed either into the room or into the spirometer. Samples of air for analysis are drawn off through an opening at the top of the spirometer bells. The gas analyses are made with the well known Haldane apparatus.

Technic of Experiments.—The subject is brought to the laboratory and allowed to rest for thirty or forty minutes. He then assumes a comfortable position in a chair and the small table is so adjusted that the rubber mouthpiece connected with the respiratory valve can be held in the mouth with a minimum of muscular effort. The nose is closed with an ordinary nose clip; the subject now inspires from the large spirometer filled with room air and expires through the three way valve into the room. This preliminary period in which from fifty to sixty liters of air are breathed affords the subject time to accustom himself to the experimental conditions. After inspecting the respiratory valves and other parts of the apparatus, the time is noted and the expired air is allowed to enter the spirometer. The experiment is continued usually for five minutes or less, depending on the minute volume of the subject's respiration. The nose clip and mouthpiece are now removed and the subject breathes naturally until the next experiment. This interval is about fifteen minutes during which the analysis of the expired carbon dioxid is made and the inspiratory spirometer is filled with a new mixture and analyzed. At least two observations at room air are first made to see that the carbon dioxid output is fairly constant. Other experiments with various percentages of carbon

dioxid in the inspired air are then made. Sufficient amounts of oxygen have always been added to maintain its concentration in the inspired at approximately 20 per cent.

Respiratory Response to Carbon Dioxid.—The results obtained on the two normal individuals are presented in Table 1. These data show the approximate variations that have been found in normal resting persons after they have become accustomed to the experimental conditions. Even individuals such as medical students who understand the purpose of the experiments are very likely to over-ventilate at the first few observations. The same is, of course, true of hospital patients, but after a little experience constant results are obtained.

TABLE 1.—THE RESPIRATORY RESPONSE TO INCREASING PERCENTAGES OF CARBONDIOXID IN THE INSPIRED AIR IN TWO NORMAL SUBJECTS

Inspired Air	Period Observed, Min.	Total Volume Expired Air, Liters	Minute Volume Expired Air, Liters	Carbon Dioxid				Respiratory Rate per Min.
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Subject C. P. H.								
Room air	5	25.5	5.1	4.40	224	0	224	6
Room air	5	25.0	5.0	4.64	232	0	232	7
1.7% CO_2	5	35.5	7.1	5.12	363	120	243	8
3.04% CO_2	5	44.0	8.8	5.44	479	268	211	10
4.3% CO_2	4	48.0	12.0	5.84	701	540	161	13
6.16% CO_2	3	58.5	19.5	7.04	1,373	1,201	172	17
7.2% CO_2	2	70.0	35.0	7.00	2,000	2,520	140	25
Subject P. J. C.								
Room air	5	35.0	7.0	3.44	241	0	241	17
Room air	5	35.0	7.0	3.40	238	0	238	17
1.92% CO_2	5	40.0	8.0	4.32	346	154	192	15
4.0% CO_2	5	56.0	11.2	5.76	645	448	197	15
6.0% CO_2	3	52.5	17.5	7.00	1,225	1,050	175	17
7.12% CO_2	2	44.0	22.0	7.84	1,725	1,500	150	18
8.40% CO_2	2	64.0	32.0	8.80	2,816	2,688	128	22

Table 2 contains the results of two experiments on Eli B., a patient with chronic pulmonary emphysema. The experiment made April 5 was done shortly after his admission to the hospital and shows a sluggish respiratory response to inspired carbon dioxid. Similar results were obtained in the experiment done five months later (Sept. 13). A comparison of these two experiments shows the constancy with which the abnormal response to carbon dioxid is maintained. A further illustration of this is given by the data in Table 3. These experiments were performed several months apart on Peter M. This patient has been in the hospital all this time and frequent observations at intervals have yielded similar results. His respiratory response to carbon dioxid and that of the normal subject, P. J. C., is shown graphically in Figure 2.

After observing the respiratory response to carbon dioxid in normal individuals and particularly in patients with heart disease, the subjects

TABLE 2.—The Respiratory Response to Increasing Percentages of Carbon Dioxid in Eli B., a Patient with Chronic Pulmonary Emphysema

Inspired Air	Period Observed, Min.	Total Volume Expired Air, Liters	Minute Volume Expired Air, Liters	Carbon Dioxid				Respiratory Rate per Min.
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Experiment 1 April 5, 1919								
Room air	5	45.0	9.0	3.88	349	0	349	17
Room air	5	44.5	8.9	3.84	342	0	342	18
1% CO_2	5	45.5	9.1	4.22	393	91	302	19
2.32% CO_2	3	27.5	9.2	5.44	500	213	287	18
5.52% CO_2	4	44.0	11.0	7.52	827	607	220	18
7.08% CO_2	3	42.5	14.2	8.68	1,233	1,005	228	19
8.00% CO_2	3	50.0	16.6	9.32	1,547	1,328	219	21
9.12% CO_2	3	57.0	19.0	10.32	1,990	1,732	258	22
Experiemnt 2 Sept. 13, 1919								
Room air	5	40.0	8.0	4.20	336	0	336	11
Room air	5	37.5	7.5	4.28	321	0	321	12
1.0% CO_2	4	35.0	8.8	5.12	450	140	310	15
3.84% CO_2	4	36.0	9.0	6.80	612	346	266	12
6.32% CO_2	3	37.5	12.5	8.40	1,050	790	260	18
7.00% CO_2	3	36.5	12.2	8.80	1,074	854	220	14
8.32% CO_2	3	44.0	13.7	9.68	1,326	1,140	186	15
9.50% CO_2	3	49.5	16.5	10.64	1,756	1,568	188	17

TABLE 3.—The Respiratory Response to Carbon Dioxid on Different Dates in Peter W., a Patient with Chronic Pulmonary Emphysema

Inspired Air	Period Observed, Min.	Total Volume Expired Air, Liters	Minute Volume Expired Air, Liters	Carbon Dioxid				Respiratory Rate per Min.
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Experiment 1 Feb. 22, 1919								
Room air	5	37.5	7.5	3.84	288	0	288	20
Room air	5	39.5	7.9	3.48	275	0	275	20
1.96% CO_2	5	39.0	7.8	4.88	381	153	228	20
3.92% CO_2	5	49.0	9.8	6.16	604	384	220	21
6.08% CO_2	4	42.5	10.6	7.88	835	644	191	21
7.28% CO_2	3	33.5	11.2	8.88	994	815	179	21
8.30% CO_2	3	34.5	11.5	9.80	1,127	961	166	21
9.60% CO_2	3	35.0	11.7	10.92	1,278	1,123	155	21
Experiment 2 Sept. 16, 1919								
Room air	5	37.5	7.5	4.24	318	0	318	20
Room air	5	42.0	8.4	3.76	314	0	314	18
2.64% CO_2	7	68.5	9.8	5.40	529	259	270	21
3.92% CO_2	5	53.0	10.6	6.32	670	415	255	21
4.90% CO_2	5	58.5	11.7	7.44	870	580	290	20
6.44% CO_2	5	61.0	12.2	8.60	1,049	785	264	21
7.52% CO_2	4	53.5	13.4	9.53	1,250	1,008	242	22
10.45% CO_2	2	28.0	14.0	11.30	1,639	1,515	124	20
Experiment 3 Oct. 5, 1919								
Room air	5	51.5	10.3	3.20	330	0	330	22
Room air	5	51.5	10.3	3.24	334	0	334	22
4% CO_2	3	33.5	11.2	6.16	690	448	242	22
6.12% CO_2	3	35.5	11.3	8.04	949	722	227	22
8.08% CO_2	3	38.5	12.8	9.76	1,249	1,034	215	22
9.28% CO_2	3	39.5	13.2	10.56	1,394	1,225	169	21
10.24% CO_2	3	42.0	14.0	11.56	1,618	1,434	184	22
11.44% CO_2	3	42.0	14.0	12.48	1,747	1,607	145	22

with emphysema afford a very sharp contrast. The ease and apparent comfort with which emphysematous patients inspire high percentages of carbon dioxid (from 8 to 10 per cent.) for short periods is very striking. This is, of course, true only up to a certain percentage, which might be called the tolerance level. At or a little above this level, symptoms of acute distress develop quite abruptly. There is

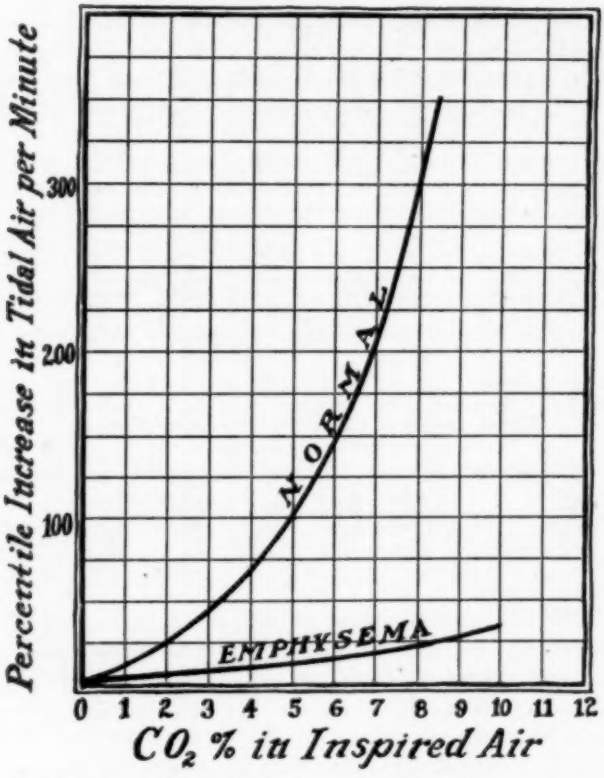

Fig. 2.—This shows the percentile increase in tidal air per minute as the percentage of inspired carbon dioxid is raised. Note that when the normal subject inspires air containing 8 per cent. carbon dioxid, the tidal air is increased about 300 per cent. and in the emphysematous subject only about 25 per cent.

headache, nausea, dizziness and the subject refuses to continue the experiment. This appearance of acute distress at a certain concentration of inspired carbon dioxid is quite characteristic and was noted in all experiments where high percentages were breathed for short periods (from 10 to 15 minutes). Take, for example, experiment 3

in Table 3, which was done particularly to find the tolerance level. While inspiring 9.28 per cent. carbon dioxid the subject was apparently comfortable and made no complaint. Breathing 10.24 per cent. carbon dioxid caused a little dizziness, but the next observation with 11.44 per cent. caused considerable distress and it was with much effort on the part of the subject that the experiment was continued to the end. At this high concentration the minute volume was 14 liters. This and other experiments have indicated that 14 liters per minute is the maximum volume of air which this subject can exchange. In other words, with a potent stimulus to respiration he has a factor of safety amounting to about 7 liters per minute as compared with about 50 liters for normal persons under the same conditions. This indicates a marked limitation in pulmonary reserve. It also shows how helpless the emphysematous subject is to combat an accumulation of carbon dioxid in the body occurring when metabolism is increased as in exercise, or when the resting metabolic carbon dioxid is retained as happens when air rich in carbon dioxid is inspired.

For a given concentration of inspired carbon dioxid the emphysema subjects take less carbon dioxid into the lungs per minute. This is obviously due to the difference in minute volume in the two cases. For example, Peter W. (Table 3) breathing 10.15 per cent. carbon dioxid actually took int the lungs less carbon dioxid per minute than the normal subject, P. J. C. (Table 1), breathing 7.12 per cent. carbon dioxid. It is further noted in both the normal and emphysematous subjects that as the per cent. of inspired carbon dioxid rises, the excess of carbon dioxid output over intake falls. These figures are obtained by simply subtracting the cubic centimeters of carbon dioxid inspired per minute from that expired per minute. Obviously, at room air the difference represents metabolic carbon dioxid but as increasing percentages are breathed more and more metabolic carbon dioxid is retained in the body.

The almost constant respiratory rate at all concentrations of inspired carbon dioxid, particularly in the case of Peter W. (Tables 5, 6 and 7) afford an interesting illustration of the significance of the lung elasticity in breathing. Even while respiring room air there is no time interval between one expiration and the succeeding inspiration. With a potent stimulus to respiration Peter W., is unable to inflate and deflate his lungs more than twenty-two times per minute. It is a matter of common observation that most cases of emphysema have a prolonged expiratory cycle. In both Eli B. and Peter W. expiration lasted approximately twice as long as inspiration.

In comparing the data from the experiments on the two subjects with emphysema it is noted that Eli B. was a little more sensitive to

carbon dioxid. This may have been due in part to the fact that he had a lesser grade of emphysema, as indicated by the size of the lungs and by the diminished vital capacity (Table 4).

TABLE 4.—The Vital Capacity on Different Dates in the Two Emphysematous Subjects

Eli B., Height 5 ft. 9 in.		Peter W., Height 5 ft. 10 in.	
Date	Vital Capacity, C.c.	Date	Vital Capacity, C.c.
4/ 2/19	2,600	2/18/19	1,600
4/ 5/19	2,800	4/ 6/19	1,700
4/14/19	3,200	10/ 5/19	1,750

The Carbon Dioxid Tension of the Blood.—It has been demonstrated by others that the carbon dioxid tension in the alveolar air is abnormally high in emphysema. Several experiments were done to determine the alveolar carbon dioxid, using the original Haldane and Priestly technic and also the method brought out by Pearce.[6] The results were usually well above the normal but they showed considerable variation. This was attributed to poor cooperation on the part of the subject. In order to obtain more constant results, the carbon dioxid tension in the blood was determined by analysis of the expired air brought into equilibrium with the venous blood. The method suggested by Henderson and Prince[7] was found most useful in work with patients. The technic is simple and quite consistent results were obtained in both normal and diseased individuals. With this method not only the tension of carbon dioxid in the venous blood is determined, but some information is also obtained concerning the rapidity with which equilibrium is reached between the gases of the venous blood and the air in the lungs. Here, as in the foregoing observations, the data obtained in experiments on normal individuals were used for comparison with those found in the subjects with emphysema. The technic employed was as follows: A graduated Krogh spirometer of six liters capacity is used instead of a rubber bag, as recommended by Henderson. The spirometer is preferred because it affords a means of checking the total volume of each successive expiration. The outlet to the air chamber of the spirometer is through an iron pipe, 1 inch inside diameter. Attached to this pipe is a three way steam valve, one outlet of which is connected with a rubber mouthpiece.

The subject is comfortably seated before the spirometer and the nose closed with a clip. He inserts the mouthpiece into the mouth and breathes room air normally for from twenty to thirty seconds,

6. Pearce, R. G.: Am. J. Physiol. **43**:73, 1917.
7. Henderson, Y., and Prince, M.: J. Biol. Chem. **33**:325, 1918.

through one outlet of the valve. Just at the height of a normal inspiration he is told to blow, the valve is suddenly turned so that all the expired air passes into the spirometer. When the forced expiration is completed the valve is again turned, thus closing off the spirometer. A sample of this air is now drawn off and analyzed for carbon dioxid. During this analysis the subject removes the nose clip and mouthpiece and breathes naturally. After a few minutes the mouthpiece is again taken and room air is respired through the valve outlet. At the height of a normal inspiration the subject is told to blow but this time he expires into the room. At the end of the deepest possible expiration he raises his finger as a signal, the valve is suddenly turned, and the contents of the spirometer is inspired. This is held ten seconds and forcibly expired back into the spirometer. A carbon dioxid analysis of this expired air is then made. This procedure of inspiring the contents of the spirometer—holding ten seconds and expelling—is repeated until the carbon dioxid percentage of the expired air reaches a constant level.

The same technic is used to determine the rapidity with which a high concentration of carbon dioxid (from 12 to 13 per cent.) reaches the level of carbon dioxid in the venous blood. In this case a carbon dioxid-rich air mixture is first put into the spirometer, the total volume equal to that which the subject forcibly expires after a normal inspiration. The rebreathings, as described above, are performed until a constant carbon dioxid percentage is reached in the expired air.

TABLE 5.—THE RISE IN CARBON DIOXID FROM INTERMITTENT REBREATHINGS IN TWO NORMAL PERSONS AND TWO PATIENTS WITH EMPHYSEMA

Temperature, 20 C. Barometer, 742 Mm. Hg.

Number of Intermittent Rebreathings	Percentage of Carbon Dioxid in Expired Air			
	Normal Subject	Normal Subject	Emphysema, Eli B.	Emphysema, Peter W.
1*	4.88	4.48	5.40	6.08
2	6.40	6.0	7.52	7.52
3	7.04	7.20	8.28	8.80
4	7.08	7.28	8.92	9.23
5	7.28	7.26	9.16	9.50
6	7.20	7.28	9.22	9.45
7	7.28	7.28	9.40	9.50
8	....	....	....	....

* The first analysis in each subject is the carbon dioxid content of a forced expiration after a normal inspiration of room air.

Table 5 contains the experimental data obtained in two normal individuals and two emphysematous subjects (Eli B. and Peter W.). Tables 6 and 7 show the results of taking a high percentage of carbon dioxid into the lungs and rebreathing until an equilibrium is attained. Curves plotted from these data are shown in Figure 3.

The data obtained show that, after four or five rebreathings, the carbon dioxid in the inspired air comes practically to a constant level and this occurs when a low as well as a high concentration is first taken into the lungs. Although the number of patients studied is too small to draw definite conclusions, yet the results seem to indicate that the tonometric function of the emphysematous lung is not seriously impaired. That is, under the experimental conditions, carbon dioxid equilibrium is reached between blood and lung air in approximately the same time in the emphysematous subject as in normal persons.

TABLE 6.—THE FALL IN CARBON DIOXID FROM INTERMITTENT BREATHING IN TWO NORMAL PERSONS

Temperature, 20 C. Barometer, 742 Mm. Hg.

Number of Intermittent Rebreathings (Spirometer Filled With 12.8 per Cent. Carbon Dioxid)	Percentage of Carbon Dioxid in Expired Air	
	Normal Subject	Normal Subject
1*	10.0	9.20
2	8.6	8.00
3	7.68	7.60
4	7.20	7.28
5	7.28	7.20
6	7.28	7.28
7	7.20	7.20

* The carbon dioxid content of the air forcibly expired after first filling the lungs with air containing 12.8 per cent. carbon dioxid and holding for ten seconds.

TABLE 7.—THE FALL IN CARBON DIOXID FROM INTERMITTENT REBREATHING IN A PATIENT WITH EMPHYSEMA

Temperature, 22 C. Barometer, 738 Mm. Hg.

Number of Intermittent Rebreathings (Spirometer Filled with 13 per Cent. Carbon Dioxid)	Percentage of Carbon Dioxid in Expired Air
	Emphysema, Ell B.
1*	10.24
2	9.72
3	9.50
4	9.56
5	9.56
6	9.45
7	9.45

* The carbon dioxid content of the air forcibly expired after first filling the lungs with air containing 13 per cent. carbon dioxid and holding for ten seconds.

It is apparent that such observations throw little light on the facility with which carbon dioxid can be eliminated from the body, because such important factors as the blood flow through the lungs, the available alveolar surface, and the efficiency of alveolar ventilation are not considered. The level at which carbon dioxid equilibrium is established is definitely higher in emphysema than in the normal.

Observations on several normal persons at rest have shown that the venous carbon dioxid as determined by the technic described above, varies between 7 and 7.4 per cent. at 20 C. and the prevailing barometric

pressure, 740 mm. Hg. Under similar experimental conditions the results have been consistently high in both Eli B. and Peter W. A few determinations of the alveolar carbon dioxid on these patients have also been high. Such abnormally high figures admit of two interpretations.

The carbon dioxid content of the venous and arterial pulmonary air (Y. Henderson) as estimated either does or does not represent the level of free carbon dioxid in the pulmonary venous and arterial blood respectively. There is little in favor of the negative side of the

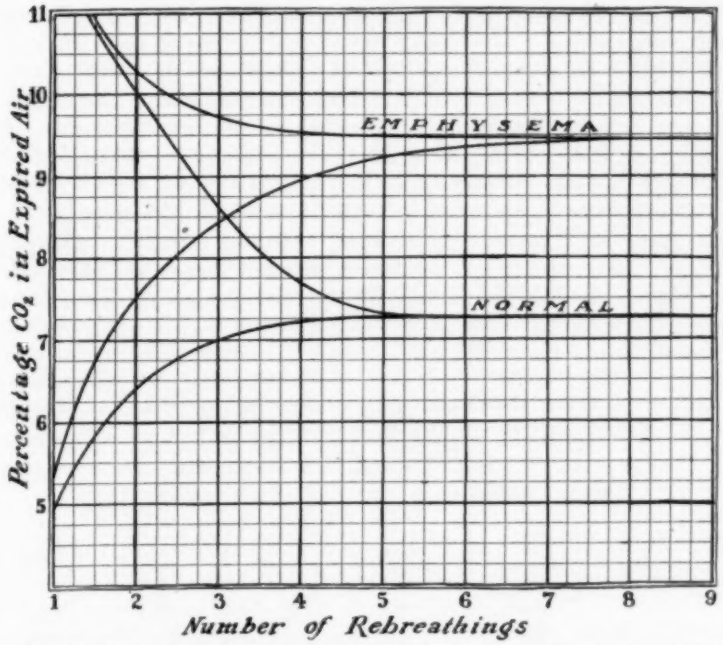

Fig. 3.—Curves plotted from experimental data to show the level at which equilibrium is established between the carbon dioxid of the lung air and the carbon dioxid tension of the venous blood in the normal and emphysematous subjects.

question unless one assumes that the methods for obtaining samples of the lung air are unreliable. On the other hand, as pointed out by Bohr, and particularly by Krogh,[8] the diffusion constant (the diffusion at 1 mm. tension difference during 1 minute, in cm. at 0 degrees 760 mm.) for carbon dioxid is such as to render the tension of this gas the same on the two sides of the pulmonary membrane. To study

8. Krogh, A.: Skand. Arch. f. Physiol. **23**:248, 1910.

this question, H-ion concentration (p_H) and total carbonate determinations were made on the arterial and venous bloods of the emphysematous subjects. The data from the bloods of normal persons at rest served as controls.

The arterial blood was obtained by direct puncture of the radial artery, using a similar technic as that employed by Stadie.[9] The venous blood was collected without stasis from one of the large veins at the bend of the elbow. Both samples of blood were delivered under oil into paraffiin coated centrifuge tubes and immediately centrifuged at high speed. A little oxalate was added to prevent clotting. One c.c. of the separated plasma was delivered under carbon dioxid free ammonia water in the receiving cup of the Van Slyke apparatus and the total carbon dioxid content determined directly. This direct method appears to have certain advantages over the widely used technic of first exposing the plasma routinely to 5.5 per cent. carbon dioxid and determining the carbon dioxid combining power. It is simpler and with care taken to prevent the loss of carbon dioxid it gives results obviously more representative of the carbon dioxid content of the circulating blood particularly when one is dealing with pathologic conditions. Reference to and the data obtained in normal and pathologic individuals by the use of this direct method were presented in a preliminary report.[10] Recently Van Slyke and Stadie[11] have recommended its adoption.

TABLE 8.—Total Carbonate Content of the Arterial and Venous Plasma and Ph of the Whole Blood (Arterial) in Five Normal Subjects and Two with Emphysema

Normal Individuals			Emphysema*		
Carbon Dioxid Reduced to 0 C. 760 Mm. in 100 C.c. Plasma		P_H Arterial Blood	Carbon Dioxid Reduced to 0 C. 760 Mm. in 100 C.c. Plasma		P_H Arterial Blood
Arterial, C.c.	Venous, C.c.		Arterial, C.c.	Venous, C.c.	
57.8	64.4	7.35	76.1	82.7	7.4
59.1	67.2	7.4	74.1	78.4	7.4
57.5	61.5	7.4	80.2	88.4	7.45
51.5	59.9	7.35	74.5	80.2	7.35
58.4	60.0	7.40	71.0	76.0	7.4

* Determinations made on different dates over a period of several months.

Table 8 contains the data for the total carbon dioxid content of the arterial and venous plasma along with the p_H of the whole arterial blood as drawn. The results on five normal individuals at rest are given to compare with similar data obtained at different dates on Eli B., and Peter W.

9. Stadie, W. C.: J. Exper. Med. **40**:215, 1919.
10. Scott, R. W.: Proc. Soc. Exper. Biol. & Med. **17**:18, 1919.
11. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **41**:191, 1920.

It is seen that the total carbonate content of both the arterial and venous plasma in emphysema is distinctly above normal, while the H-ion concentration (p_H) of the whole blood as drawn is not appreciably changed. Only one interpretation can be placed on such results in view of the well established relation between the free and combined carbon dioxid to the H-ion concentration in blood. Associated with a high carbonic acid content there is a corresponding increase in the sodium bicarbonate so that the ratio $\frac{H_2CO_3}{NaHCO_3}$ and hence the H-ion concentration is maintained at appreciably a normal level.

DISCUSSION

It is clear from the data presented that a subject with chronic pulmonary emphysema will inspire relatively high percentages of carbon dioxid for several minutes with only small increases in the minute volume over that at room air. In interpreting this, attention must first be directed to the question of whether or not the carbon dioxid taken into the lungs under the experimental conditions, actually caused a retention of metabolic carbon dioxid. From the physical laws of diffusion there must be a slight pressure gradient from the blood to the lung air. If the carbon dioxid tension in the lungs is elevated, as was done in the foregoing experiments, the metabolic carbon dioxid is retained in direct proportion to this elevation. The data indicates this to be the case in emphysema as well as in the normal. There are, of course, variations in individual experiments, but, as a rule, increasing percentages of carbon dioxid in the inspired air cause a progressive drop in the metabolic output.

When this fact was first obtained it seemed quite paradoxical to assume that the subjects with emphysema possessed an increased tolerance to carbon dioxid particularly in view of the fact that they were distressed with slight exercise. Later, experiments were conducted to test the tolerance limit, when it was found that there was a fairly definite concentration at which the subject developed acute symptoms such as headache, nausea, dizziness, etc. Further study of this point indicated that the "break" in emphysema depended on two factors, i. e,, the concentration of the inspired carbon dioxid and the length of the breathing period. For example, Peter W. developed acute distress in ten minutes breathing 11.4 per cent. carbon dioxid. A similar "break," although not so sharp, occurred while breathing 6.8 per cent. carbon dioxid for twenty minutes. An attempt was made to find a definite inverse ratio between inspired carbon dioxid and time of inhalation by having the subject inspire various concentrations until symptoms of intolerance developed. The results showed clearly, as would be expected, that as the percentage of inspired carbon dioxid

was elevated the time required to produce signs of intolerance diminished, but no definite constant (carbon dioxid inspired multiplied by length of breathing period) was obtained. The failure to obtain such a constant was due in part to the difficulty of recognizing the "break" with low concentration, particularly in the longer experiments, since it is necessary to depend on the patient's subjective sensations.

It is apparent from the foregoing that the length of the breathing period must be kept reasonably constant in contrasting the normal with the emphysema. However, when this factor is controlled, comparison of the data shows a sluggish response in the case of emphysema (Fig. 2). Two possibilities are suggested for this: (1) an increased capacity for storage of carbon dioxid in the body fluids; (2) a change in the sensitivity of the respiratory center. It is conceivable that the functional activity of the respiratory center may be depressed in emphysema through a slow process of adaptation. Observations bearing on this phase of the subject are under way but sufficient facts are not at present available to warrant any definite conclusions.

Evidence suggesting an increased capacity for binding carbon dioxid is afforded by the high level of blood bicarbonate (Table 8). As the buffer value of body fluids is proportional to the bicarbonate content, it appears that up to a certain limit, the emphysema subject can bind more carbon dioxid than the normal. Consequently, higher percentages of the gas may be inspired before a change occurs in the H-ion concentration in the blood of sufficient magnitude to stimulate the respiratory center. This seems to account in part for the sluggish respiratory reaction observed.

The fact that the addition of carbon dioxid to blood raises not only the carbonic acid, but also the sodium bicarbonate content was first recognized by Zuntz. Later Gürber studied the question and concluded that carbon dioxid caused a passage of chlorids from the plasma into the corpuscles. Recently Fridericia [12] confirmed the work of other investigators by showing that as the carbon dioxid tension of blood is elevated, the carbon dioxid combining power of the plasma and the red cells is also raised. His results indicate further that the increased carbon dioxid combining power of the plasma is due chiefly to the passage of chlorid ions from the plasma into the corpuscles. The sodium thus liberated in the plasma combines with carbon dioxid to form more bicarbonate.

Experimental proof that the blood bicarbonate was elevated was obtained by me [13] in cats made to breathe varying concentrations of

12. Fridericia, L. S.: J. Biol. Chem. **42**:245, 1920.
13. Scott, R. W.: Am. J. Physiol. **44**:196, 1917.

carbon dioxid. This was later confirmed by Henderson and Haggard [14] On the other hand, there is much experimental and clinical evidence to show that the blood bicarbonate is diminished when acids other than carbon dioxid are added to the blood. It is clear, therefore, that the tissue carbonate is no fixed quantity, but may undergo wide variations, the H-ion concentration being maintained within normal limits. This was recently emphasized by Henderson and Haggard.[15] They showed from animal experiments that there were four theoretical alterations in the normal free and combined carbon dioxid content of the blood. One of these, in which carbonic acid and sodium bicarbonate are both at a high level but the normal ratio is apparently maintained, is illustrated in emphysema. The progressive degenerative process in the lungs in this condition causes an increasing impediment to alveolar ventilation, with the consequent interference with gaseous exchange. This ultimately leads to a retention of carbon dioxid as well as a certain amount of chronic anoxemia. The high level of free carbon dioxid of the blood in emphysema is attained gradually so that ample time is afforded for the development of compensatory mechanisms. The maintenance of the body bicarbonate at a permanent high level appears as one important illustration. This enables the emphysematous subject to tolerate a high carbon dioxid tension in the blood normally and also affords a certain protection against undue fluctuations in H-ion concentration which might otherwise occur from metabolism. Considering the body bicarbonate as a chemical factor of safety, it appears that the emphysema subject can tolerate for short periods higher concentrations of inspired carbon dioxid than the normal. When, however, the tissue buffer is exceeded, there is little mechanical factor of safety as represented by pulmonary ventilation and acute distress develops suddenly. The normal subject on the other hand has a considerable pulmonary reserve and compensates for carbon dioxid retention by increasing ventilation. Consequently no sudden "break" occurs but discomfort develops gradually.

SUMMARY

1. Two patients with chronic pulmonary emphysema of the socalled "large lunged" type have been studied over a period of several months and compared with normal persons as controls.

2. It was found that the emphysematous patients breathed high percentages of carbon dioxid (from 8 to 10 per cent.) for ten and fifteen minute periods with relatively little increase in the minute volume, and without subjective symptoms of distress. Slightly higher

14. Henderson, Y., and Haggard, H. W.: J. Biol. Chem. **33**:343, 1917.
15. Henderson, Y., and Haggard, H. W.: J. Biol. Chem. **39**:163, 1919.

percentages were intolerable and caused a sharp "break" with symptoms of acute distress such as headache, nausea and dizziness. The concentration of inspired carbon dioxid necessary to produce signs of intolerance was found to vary inversely with the length of the breathing period.

3. There was a definite elevation in the free and combined carbon dioxid of the blood in emphysema, but the ratio $\frac{H_2CO_3}{NaHCO_3}$ was such as to maintain the H-ion concentration within normal limits.

4. It is suggested that the increased buffer of the body fluid in emphysema compensates to some extent for the impairment of pulmonary ventilation and offers a certain protection against undue fluctuations in H-ion concentrations which might otherwise occur.

OBSERVATIONS ON THE CHEMICAL PATHOLOGY OF THE BLOOD IN PERNICIOUS ANEMIA AND OTHER SEVERE ANEMIAS *

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INTRODUCTION

This study is confined to fundamental chemical conditions of the blood in pernicious and severe secondary anemia and, for comparison, to a study of the same conditions in one series of normal subjects and in another series of pathologic conditions other than anemias. We found early in our study that the total blood solids in clearly diagnosed cases of pernicious anemia were extraordinarily low. From the comparison series above mentioned it appeared that so great an abnormal deviation is so uncommon an occurrence in other pathologic conditions as to make extremely low blood solids one of the pathologic characteristics of pernicious anemia and severe secondary anemia. Further observation showed marked deviation from normal values in the total nitrogen of the whole blood in this condition but a much less pronounced deviation in the total nitrogen of the plasma. However, on studying the ratio of the whole blood nitrogen to the total nitrogen of the plasma a relation ("index" in column 7 of Tables 1, 2 and 3) appeared that is also a pathologic characteristic of severe anemia. There is reason to believe that this abnormal index and the excessively low blood solids are as constantly associated chemical conditions of severe anemias as the low red cell count is characteristic of the morphology of this blood. We regard the present study as introductory and we are making further observations on these conditions.

METHODS

The methods used were an application of the principles developed in a previous publication [1] but some deviations from the technic there described and some corrections were made. There is also added the following method for the determination of total plasma nitrogen, which obviates the difficulty of separating such small amounts of plasma as are here used, from corpuscles. The technic for blood solids was used as described.[1]

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1. Peters, Amos W.: The Micro Determination of Nitrogen by Direct Nesslerization and of Total Solids, in Drop Quantities of Human Blood, J. Biol. Chem. **39**:295, 1919.

For whole blood and plasma nitrogen the blood was collected in one weighed and stoppered test tube containing exactly 12 c.c. of fluorid-salt solution of the following composition: sodium fluorid, 3.5 gm.; sodium chlorid, 5.0 gm. per 1,000 c.c. distilled water. The alkalinity to phenolphthalein of 1,000 c.c. or more should be neutralized by adding concentrated hydrochloric acid, one drop at a time, until a test remains colorless with the indicator. Enough of the 10 per cent. sodium hydroxid used elsewhere in these methods should then be added drop by drop from the buret to just restore the alkalinity to phenolphthalein as found on a test sample of the medium. Without the precaution of regulating the reaction of the fluorid-salt medium the results obtained for plasma nitrogen might be vitiated entirely by solution or extraction of corpuscles. The first two drops of finger blood and no subsequent ones, were received in the previously described test tube which was then reweighed to ascertain by difference the weight of the blood. From this total volume two aliquots of 2 c.c. each, designated A 1 and A 2, respectively, were removed for the determination of the total nitrogen of the whole blood. Care should be taken to mix thoroughly the contents before each aliquot is taken in order to avoid error from partial sedimentation of corpuscles, which occurs rapidly. The remaining volume is transferred to a conical centrifuge tube and centrifuged thirty minutes. The clear and nearly always colorless liquid is decanted from the corpuscles into another tube from which 5 c.c., designated as AA, is removed for the determination of the total nitrogen of the plasma. This 5 c.c. is, of course, an aliquot of the original volume.

The two drops of blood usually weigh from 50 to 70 mg., and the total volume of the original blood dilution may be taken at e. g. $V = 12.07$ c.c., from which aliquots of $2./12.07$ and $5./12.07$ have been taken of the weight of the two drops of blood.

If a nonprotein determination is also desired, the ten or more drops of finger blood next following the first two are received in about 10 c.c. of distilled water (not in sodium fluorid solution as directed in the previous publication [1]) and this is designated as B. The tube for total solids being designated as C, an entire set of determinations consist of A 1, A 2, AA, B and C. The nitrogen in A 1, A 2 and AA is determined as previously described [1] except as the following modifications have much improved the process.

All neutralized unknown solutions that are to be nesslerized are first made to a volume of 40 c.c. in a 100 c.c. cylinder, from which the liquid is delivered into 10 c.c. of the below described Nessler solution, which has been measured with a volumetric pipet into a carbon dioxid flask. The final volume is thus 50 c.c. without further

measurement or transfer and the Nessler reaction always occurs under comparable conditions of concentration. When a series of determinations is to be made it is advantageous to let the several cylinders, each made to a volume of 40 c.c., stand in a row, with carbon dioxid flask with the measured 10 c.c. of Nessler standing beside each, until the operator is ready to do the whole series of nesslerizations and colorimetric readings in order.

The modified Nessler reagent is made by mixing 200 c.c. of the Folin [2] potassium-mercuric iodid stock solution with 100 c.c. of 10 per cent. sodium hydroxid and 200 c.c. of distilled water. With this modification the progressive change in color immediately after mixing as above is less rapid. By making the colorimetric reading against the permanent color standard, in the interval between four and seven minutes after mixing, the agreement between duplicates on the same reagents can be kept within a few tenths of a millimeter. Duplicates on blood also show exceedingly small deviations.

TABLE 1.—NORMAL HUMAN BLOOD

1 Blood No.	2 Subject No.	3 Date	4 Solids, per Cent.	5 Whole Blood N, per Cent.	6 Plasma N, per Cent.	7 Index Whole Blood N % / Plasma N %
1	1	10/ 7/19	20.6	3.16		
2	1	10/27/19	20.3	3.45	0.74	4.7
3	1	11/11/19	20.8	3.00	0.66	4.5
38	1	12/24/19	....	3.34	0.60	5.6
42	1	5/ 6/20	....	2.78	0.81	3.4
45	2	6/ 1/20	....	3.18	0.88	3.6
46	2	6/ 4/20	....	3.29	0.82	4.0
47	2	6/29/20	....	2.86	0.83	3.5
59	2	7/ 2/20	20.4	2.83	0 96	2.9
60	2	7/13/20	....	3.26	0.78	4.2
48	3	6/ 3/20	....	3.33	1.05	3.2
49	3	6/ 9/20	....	3.36	1.14	2.9
50	3	6/25/20	22.6	2.73	1.08	2.7
51	3	6/30/20	....	2.90	0.92	3.2
57	3	7/ 2/20	19.1	2.73		
58	3	7/ 2/20	....	2.84	1.08	2.6
61	3	7/10/20	22.4	2.65	1.06	2.5
62	3	7/13/20	18.8	2.85	0.85	3.4
52	4	6/ 8/20	....	3.22	1.06	3.0
53	4	6/25/20	22.8	3.14	0.82	3.8
54	4	6/30/20	20.8	2.94	0.92	3.2
55	5	6/16/20	....	3.15	1.13	2.8
Average index						3.5

The same stock quantity of distilled water and the same stock of reagents should be used throughout a given series of determinations that are to be calculated by means of a given base value (0.35 mg. N). It is well worth noting from the standpoint of accuracy in dealing with such small amounts of nitrogen as are used that this base value always functions as a blank on the reagents, including the distilled water, as well as being the base of calculation.

2. Folin, O., and Dennis, W.: Nitrogen Determination by Direct Nesslerization. I. Total Nitrogen in Urine, J. Biol. Chem. **26**:479, 1916. Folin, O., and Hsien, Wu: A System of Blood Analysis, J. Biol. Chem. **38**:89, 1919.

Pebbles or other means to prevent bumping during the digestions have been found unnecessary except for nonprotein nitrogen.

The value of R used in the calculation of the colorimetric reading into mg. of nitrogen was determined for each series of unknowns by comparing the results of a single test each on 0.35 mg. and 0.15 mg. standard nitrogen.

With the above modifications we have found the use of a single constant color standard, which is the special characteristic of this method, not only accurate as previously described, but also quite expeditious when many determinations were to be made as in these experiments. This is due to the elimination of the time and labor consumed in the customary procedure of making a fresh standard for each and every determination.

TABLE 2.—BLOOD IN PERNICIOUS ANEMIA AND IN SECONDARY ANEMIA

1 Blood No.	2 Case No.	3 Date	4 Solids, per Cent.	5 Whole Blood N, per Cent.	6 Plasma N, per Cent.	7 Index = Whole Blood N % / Plasma N %	8 Diagnosis
15	1	10/ 9/19	13.0	2.34			
16	1	10/11/19	12.7	1.77	1.14	1.6	Pernicious anemia and syphilis
17	1	10/18/19	13.2	2.10	1.19	1.8	
18	1	10/29/19	12.0	2.12	1.25	1.7	
19	2	11/ 1/19	12.6	1.99	0.99	2.0	
20	2	11/ 4/19	12.6	2.03	0.82	2.5	Chronic secondary anemia
21	2	11/ 6/19	13.5	1.97	1.05	1.9	
35	3	12/ 9/19	8.0	1.34	0.90	1.5	
36	3	12/11/19	9.8	1.43	0.73	2.0	
39	3	12/27/19	10.1	1.29	0.76	1.7	Pernicious anemia
44	3	5/20/20	....	2.00			
65	3	7/17/20	14.7	2.17	1.09	2.7	
23	4	11/18/19	14.5	2.70	0.97	2.8	Pernicious anemia
40	5	4/27/20	....	1.38	1.01	1.4	Pernicious anemia
41	6	4/30/20	9.0	2.16	1.02	2.1	Secondary anemia
63	7	7/16/20	12.3	2.25	0.74	3.0	Exophthalmic goiter and sec. anemia
66	8	7/21/20	13.6	2.37	1.04	2.2	Suspected pernicious anemia
Average index						2.1	

CLINICAL DATA ON CASES IN TABLE 2

The clinical data recorded below were primarily intended to present only the salient pathologic conditions that might stand in relation to the factor of anemia. We, however, doubt that such a selection is justifiable in view of the possible interrelations of all pathologic conditions in the same subject. We have, nevertheless, selected the trio of conditions that are commonly regarded as constituting the essentials of the syndrome of pernicious anemia, i. e., the blood count, the gastro-intestinal-abdominal findings and the neurologic factor. These include the low red cell count, the achlorhydria, and the evidences of cord degeneration, all of which, it should be remembered, need not be concurrent, especially the cord symptoms. After having

made this selection, and after some reflection on what might be the consequences of the conditions revealed by the laboratory findings, we were much impressed by the almost constant finding, in the physical examination, of more or less pronounced edema in nearly all these anemia cases whether pernicious or secondary. Minor functional but not organic cardiac symptoms and a palpable liver and spleen were practically constant concomitants of the edemas. Whether these edemas are to be regarded as primarily due to mechanical, obstructive factors or to chemical alterations of blood composition or of vascular endothelium is not answered by our present study

TABLE 3.—HUMAN BLOOD IN PATHOLOGIC CONDITIONS (OTHER THAN PERNICIOUS ANEMIA)

1 Blood No.	2 Case No.	3 Date	4 Solids, per Cent.	5 Whole Blood N, per Cent.	6 Plasma N, per Cent.	7 Index. Whole Blood N % / Plasma N %
13	1	11/15/19	....	1.29	0.71	1.5
14	2	11/13/19	19.3	3.21	0.80	4.0
26	3	12/11/19	16.0	2.74	0.67	4.1
4	4	9/30/19	18.4	2.71		
5	4	10/ 7/19	18.0	2.27		
6	4	10/16/19	18.9	2.78	0.88	3.4
7	4	10/24/19	18.8	3.15	0.62	5.1
8	5	10/ 2/19	18.0	2.75		
9	5	10/ 3/19	18.8	2.74		
10	5	10/14/19	18.8	2.80	0.81	3.5
11	5	10/22/19	19.3	3.12	0.98	3.2
12	6	10/29/19	15.7	2.31	0.64	3.6
31	7	12/16/19	20.9	3.30	0.66	5.0
37	7	12/18/19	19.0	2.63	0.65	4.0
24	8	11/20/19	20.4	2.91	0.76	4.0
43	9	5/20/20	18.4	3.13		
56	10	7/ 9/20	17.5	2.70	0.64	4.2
Average index						3.8

All hemoglobin determinations were made according to Sahli.

Differential blood counts were used in making the diagnosis of pernicious anemia.

REPORT OF CASES

CASE 1.—Male, half Indian, half Mexican, aged 40.
Diagnosis.—Pernicious anemia and syphilis.
Blood Counts:

Date 1919	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
June 5	20	800,000	4,600
June 6	18	770,000	2.950
June 18	20	870,000	6,500
June 26	19	830,000	4,500
July 8	36	1,460,000	2,600
July 21	35	1,900,000	2,100
July 31	28	2,150,000	4,500
Aug. 26	46	2,600,000	3,700
Sept. 6	60	1,780,000	.....
Oct. 5	40	870,000	.....
Oct. 14	..	1,700,000	.....
Nov. 25	..	1,456,000	.....

Gastro-Intestinal and Abdominal Symptoms.—Epigastric pain; sour stomach; constipation; fluid in peritoneal cavity, moves to dependent portion, fluctuates; liver palpable three fingers' width below costal margin; hepatic region very tender.

Neurologic Symptoms.—Practically negative.

CASE 2.—Male, Mexican, aged 38.

Diagnosis.—Chronic secondary anemia.

Blood Counts:

Date 1919	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
Oct. 30	50	1,640,000	7,700
Nov. 2	45	2,700,000	8,400
Nov. 7	45	2,200,000	8,100
Nov. 8	..	.....	7,000
Nov. 20	55	2,464,000	15,500
Nov. 25	..	3,160,000	.....

Gastro-Intestinal and Abdominal Symptoms.—Practically negative.

Neurologic Symptoms.—Negative.

CASE 3.—Male, American, aged 50.

Diagnosis.—Pernicious anemia.

Blood Counts:

Date 1919	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
Dec. 6	20	530,000	2,900
Dec. 7	12	600,000	2,600
Dec. 11	9	405,000	2,300
Dec. 12	17	665,000	2,400
Dec. 13	17	900,000	1,600
Dec. 15	..	670,000	2,100
Dec. 18	15	520,000	2,400
Dec. 21	17	600,000	2,300
Dec. 30	11	600,000	5,300
1920			
May 7	35	1,270,000	3,000

Gastro-Intestinal and Abdominal Symptoms.—Pain, nausea, vomiting at times; constipation; tenderness in region of gallbladder; abdomen full and rounded, highly tympanitic; no fluid; liver above costal margin; spleen palpable.

Neurologic Symptoms.—Pain and twitching of legs and arms, numbness; progressive weakness until unable to stand or walk; knee jerks exaggerated; ankle clonus present; Babinski positive.

CASE 4.—Female, German, aged 40.

Diagnosis.—Pernicious anemia.

CASE 5.—Female, American, aged 32.

Diagnosis.—Pernicious anemia.

Blood Counts:

Date 1920	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
April 13	15	640,000	6,000
April 15	20	710,000	5,000
April 25	15	680,000	4,200
May 7	25	980,000	3,400

Gastro-Intestinal and Abdominal Symptoms.—Pain and bloating; abdomen very tender; constipation; achlorhydria; mass extending from epigastrium below right costal border, apparently the liver; spleen palpable about 1 inch below costal margin.

Neurologic Symptoms.—Practically negative.

CASE 6.—Male, American, aged 39.

Diagnosis.—Secondary anemia.

Blood Counts:

Date 1920	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
April 22.....	32	2,800,000	5,000
May 4.....	38	3,180,000	.....

Gastro-Intestinal and Abdominal Symptoms.—Practically negative.

Neurologic Symptoms.—Practically negative.

CASE 7.—Female, American, aged 37.

Diagnosis.—Exophthalmic goiter; secondary anemia.

Blood Count:

Date 1920	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
July 1.....	60	3,200,000	4,600

Gastro-Intestinal and Abdominal Symptoms.—Appetite poor; diarrhea; free hydrochloric acid. Abdomen: no masses; no rigidity; no tenderness; liver enlarged, palpable 2 cm. below costal margin; spleen enlarged, palpable.

Neurologic Symptoms.—Dizziness; nervousness; insomnia.

DISCUSSION OF RESULTS

A comparison of Columns 4 in the three tables shows that an extreme decrease in the total solids of the whole blood is one of the prominent characteristics of a severe anemia. The normal values as shown by Table 1 may be taken to range approximately from 19 to 22 per cent. and similar or slightly lower values are found in hospital cases other than severe anemias as shown by Table 3. These latter data are of importance in showing that it is the anemia and not other possible metabolic derangement that is responsible for the low values of Table 2. These values in pernicious anemia are so low that if they represented only or principally change in chemical composition of the blood we should expect fatal physiologic consequences. Evidently, it is the outstanding characteristic alteration of severe anemia—the decrease in the number of red corpuscles—that is responsible for the low value of the total solids. A study of the clinical data confirms this proposition. We should, however, note carefully that the possibility of considerable change in the chemical composition of the blood is not to be excluded from the conditions which prevail in severe anemia. We shall report further on these and related questions in the near future.

We then have in the diminution of total solids a chemical representation of that characteristic of anemia which has heretofore been represented only by morphologic data, i. e., the red cell count.

A comparison of Columns 5 in the three tables shows that the total nitrogen of the whole blood comports itself similarly to the total solids, showing very low values for pernicious and severe secondary anemias. In this respect also the values of Table 3 for other pathologic conditions show more deviation from the normal level of Table 1 than the solids showed. This might be expected from the almost universal presence of the anemic factor in practically all pathologic conditions. A comparison of the clinical data leads us here also to attribute the decrease in nitrogen content primarily and principally but not wholly to the low red cell count. The question is very justly raised here whether part of this result may not be due to decrease in plasma nitrogen as well as to diminished number of red corpuscles. That changes in the albumin and globulin content either absolute or relative should occur in severe anemia is both possible and probable. However, the results shown by Columns 6 of the three tables fail to show a decrease in the plasma nitrogen whether the subjects be anemic or otherwise affected. On the contrary, if the plasma nitrogen undergoes any change in the pathologic conditions represented it is in the direction of increased concentration of nitrogen. We may, with some justice, attribute this tendency to the retention of waste nitrogenous products or to altered osmotic equilibria, both of which probably occur in most pathologic conditions. Provisionally, until we have made further investigations, we believe it to be a plausible proposition that the plasma interposes, for physiologic reasons, great resistance to a diminution in its nitrogen concentration, and we believe that plasma nitrogen concentrations that approach 1 per cent. are pathologic. In this connection it should be noted that the reaction of the collection medium from which the corpuscles are centrifuged should be controlled carefully, either as previously described or otherwise, in order to avoid erroneously high results for the plasma nitrogen due to solution of some corpuscles or to extraction of nitrogenous substances from the corpuscles between the time of collection and that of decantation.

We have, then, in the whole blood nitrogen, as well as in the solids, a chemical representation of the morphologic characteristic of low red cell count. We have tested experimentally on various physiologic and pathologic conditions in human subjects the reliability of this chemical expression for anemic conditions with (unpublished) results that are fully confirmatory.

It is now possible to study the quantitative relations between the whole blood nitrogen and the plasma nitrogen since the direction

of variation of each is known. When the whole blood nitrogen undergoes pathologic change it always decreases in anemia, and we have seen that the plasma nitrogen either holds its normal value or increases. The direction variation is such that the ratio $\frac{\text{Whole Blood N, \%}}{\text{Plasma N, \%}}$ under pathologic conditions diminishes since the numerator decreases and the denominator increases or remains constant. This ratio we will call nitrogen index and it is clear that as an anemia becomes more severe this index becomes smaller. The three tables adequately show how well this index expresses these pathologic conditions as well as physiologic normality.

SUMMARY

1. Human blood from three series of persons has been examined for its concentration in (*a*) total solids, (*b*) total nitrogen in whole blood, (*c*) total nitrogen in plasma. The first series comprised physiologically normal persons, the second cases of pernicious anemia and severe secondary anemia, the third cases of various pathologic conditions other than severe anemia.

2. A method has been described for the determination of plasma nitrogen in very small amounts of blood whereby plasma and corpuscles are separated after dilution.

3. The total solids of the blood of pernicious anemia and also of severe secondary anemia show great decrease from normal values or even from that of other chronic hospital cases. This decrease is due primarily to the large diminution in number of the red corpuscles and only in minor degree to decrease in plasma solids.

4. The total nitrogen of the whole blood in pernicious anemia and also in severe secondary anemias shows, like the total solids, a great decrease from the normal values. The principal cause here also is diminution in the number of the red corpuscles.

5. The percentage of total solids and of whole blood nitrogen are the essential chemical correlates of the number of red corpuscles, i. e., there is a marked proportionality in these two independently determinable factors.

6. The total plasma nitrogen in contradistinction to the total blood nitrogen either maintains its normal limits of constancy or tends to increase in percentage above that of most normal bloods, but in any case it has no tendency to decrease its nitrogen value.

7. Since in all severe anemic conditions the whole blood nitrogen decreases while the plasma nitrogen tends to increase, the resultant ratio of the first to the second, which constitutes a nitrogen index, shows from the direction of variation in both factors a natural tendency to diminish in proportion to the severity of the anemia. This index may be used as an indicator of the state and progress of the anemic condition.

THE PATHOLOGY OF EPIDEMIC PNEUMONIA IN MICE AND GUINEA-PIGS *

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The subject of epidemic pneumonia has been receiving a great amount of attention since the recent epidemics of streptococcus pneumonia and influenzal pneumonia. There are still many unknown factors of pathogenicity, virulence, invasiveness and toxicity of micro-organisms which produce epidemic diseases. These terms commonly are used without clear distinction of meaning.[1] The difficulty of reproducing characteristic epidemic lesions or even causing infection in animals with cultures of highly specialized strains of bacteria is well known. In view of these difficulties in experimental reproduction of an epidemic disease, it has seemed possibly more profitable to study the natural processes of an animal epidemic of pneumonia, followed through its entire course of development and subsidence.

The opportunity to observe and study such an epidemic presented itself in the animal room of the U. S. Naval Hospital, Chelsea, Mass., during the late winter and early spring of 1919. Distemper and epidemic pneumonia in laboratory animals has been the subject of several valuable papers,[2] but these investigations have been directed primarily toward establishing the etiologic relationship of the *Bacillus bronchicepticus* to these diseases. Very good evidence has been presented that this bacillus is the causative micro-organism in certain common epidemics of distemper and pneumonia.

In order to interpret properly the origin and course of this animal epidemic, it is necessary to describe the location of the cages in the animal room and give the number of animals exposed to the infection. This room measured ten feet square and had three steel shelves for cages on each of two opposite sides. On one side there were only guinea-pig cages, three rows of four each. On the other side the two lower shelves held eight guinea-pig cages and the top shelf twelve mice cages. At the beginning of the epidemic there were about fifty guinea-pigs in stock. During the epidemic, three lots of a dozen each were received from outside stock, making a total of eighty-six pigs exposed to the infection. Of these it is estimated that twenty-five

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1. Topley, W. W. C.: The spread of bacterial infection, Lancet **1**:1, 1919.

2. Ferry, N. S.: A preliminary report of the bacterial findings in canine distemper, Am. Vet. Rev. **37**:499, 1910.

developed recognizable symptoms of respiratory disease; a necropsy was performed on fifteen. The mice cages were crowded together, partly placed on top of one another, contained more mice than intended for their size, and were harder to keep clean than the guinea-pig cages. There were about 150 mice in these cages at the beginning and they were being increased rather rapidly by breeding. These factors probably favored the origin of the infection in the mice. Twenty-four mice with symptoms of respiratory infection were later subjected to necropsy. Several died during the early part of the epidemic and were not examined. Many others were noted with distinct or questionable illness and recovered. A conservative estimate of the total number observed sick would be fifty.

The infection in the mice at first had the characteristics of what is commonly called distemper in animals. The sick mice were identified by the affected appearance of their eyes, there being an excessive conjunctival secretion, somewhat purulent, with swollen partly closed lids and desquamation and depilation in the surrounding epithelium. Occasionally a nasal discharge and cough were noted. There also was some indisposition and roughening of the fur. Few died during this period and bacteriologic or pathologic examinations were not made. It seemed very probable, however, from these observations and the subsequent course, that the epidemic pneumonia took origin in this manner.

The first intimation of a bronchial infection among the mice occurred a few weeks after the distemper symptoms had been noted. There had been a continuation and increase of the distemper symptoms when it was observed that a number of the mice had distinctly abnormal respirations. The breathing was more rapid than normal, but most noticeable was its deep or labored character, with heaving sides and use of accessory muscles of respiration, the effort fairly shaking the animal. These mice otherwise did not appear particularly sick. Their fur was slightly roughened and they were gaunt, but they were quite active when disturbed and were feeding. Some of these mice were isolated for a time, did not die within a week or two, so were killed and examined.

The necropsies presented constantly a firm grayish white lobular consolidation in one or more lobes, most frequently the median and cephalic lobes, rarely the larger caudal lobes which usually were the seat of a compensatory emphysema. There was no pleurisy. On gross section the dilated bronchi could be seen distinctly and a thick purulent exudate expressed from the lumen. The walls of the bronchi were thickened by a firm grayish infiltration. The smaller lobes were completely involved. The larger lobes, particularly the large

caudal lobes, frequently presented a similar grayish peribronchial infiltration along the main bronchi near the hilus, the remainder of the lobe being emphysematous.

Microscopic examination of these lungs disclosed excellent examples of purulent bronchitis, or interstitial bronchopneumonia as defined by MacCallum [3] in postmeasles streptococcus bronchopneumonia. Various stages were found. Typically the bronchi were dilated and filled with a dense polymorphonuclear exudate (Fig. 1). The mucosa tended to be a thick hyperplastic layer with very thick and long cilia, but in some places was desquamated. The bronchial walls were greatly thickened by a dense infiltration of mononuclear cells of the lymphoid variety. The thickness varied with the duration and stage of the disease and the lobe examined. A striking feature in many sections was the mononuclear cell infiltration about blood vessels, of similar character to the peribronchial infiltration.

The terminal bronchioles in these cases frequently appeared to drain areas of dense polymorphonuclear alveolar exudate. It seemed possible that the main part of the polymorphonuclear exudate found farther along in the dilated bronchi might come from these alveolar lesions, the irritant features of which would give rise to the more chronic protective mononuclear peribronchial reaction. In many places, however, a distinct passage of polymorphonuclear cells through the bronchial mucosa could be seen.

The alveoli of these lungs presented variable conditions, in addition to the focal polymorphonuclear lesion at the terminal bronchioles. There was commonly a partial or complete atelectasis of the alveoli intervening between enlarged bronchi. The exudate within these alveoli consisted chiefly of sparse mononuclear cells, some containing pigment granules, an occasional polymorphonuclear leukocyte or finely granular albuminous material. In lobes in which there was only partial hilus bronchial involvement, the alveoli of adjacent uninvolved areas were markedly emphysematous.

Such cases of purulent bronchitis continued to occur among the mice for a few weeks, with occasional deaths after an illness of several days or weeks. Most of the distinctly sick mice were killed at selected periods and examined. As the infection progressed the areas of polymorphonuclear alveolar exudate increased and the mononuclear peribronchial infiltration decreased. Rather suddenly it was noticed that the type of the disease had changed. Instead of the prolonged illness with marked respiratory symptoms and few toxic symptoms, mice were found dead in cages where routine inspection

3. MacCallum, W. G.: Pathology of pneumonia at a base hospital, J. A. M. A. **70**:1150 (April 20) 1918.

on the preceding day had not shown any affected mice. Closer inspection on succeeding days identified these fulminating cases by their inactiveness and their slow and somewhat irregular respirations.

Necropsies done on these mice with toxic symptoms and fulminating course, found dead or killed, presented constantly hemorrhagic lesions in the lungs. The hemorrhagic areas varied from a light red, mottled with air filled alveoli, to a solid very dark red color. The gross appearance was striking. The smaller and more dependent lobes

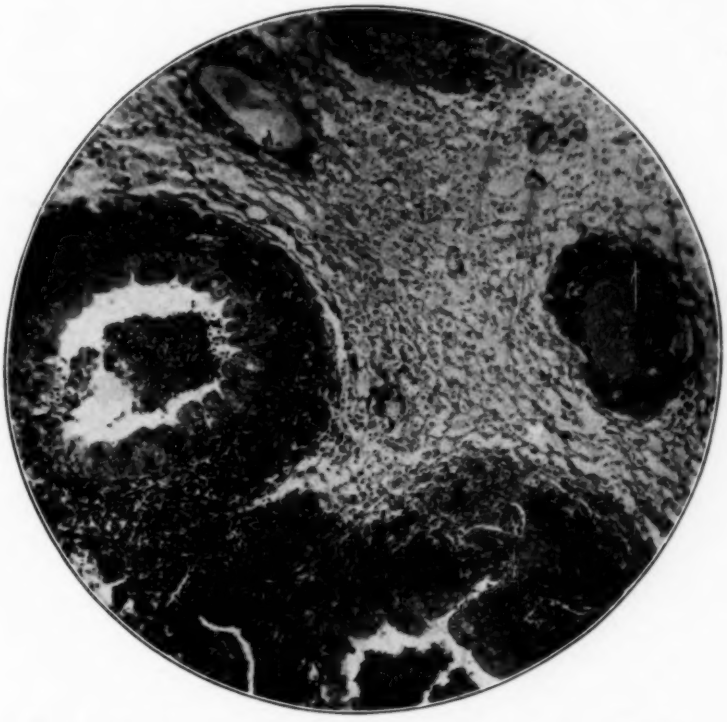

Fig. 1.—Microphotograph of a lung section from mouse 1, showing an advanced active purulent bronchitis. The bronchi are filled with polymorphonuclear leukocytes, the mucosa is hyperplastic and the wall densely infiltrated with mononuclear cells. There is a similar mononuclear perivascular infiltration. The alveoli are atelectatic, containing serum and a few mononuclear cells. Cultures gave a pure growth of the *Bacillus bronchisepticus*.

were most affected, the caudal lobes commonly being distinctly emphysematous and pink. Lobes which presented only a slight red mottling on the surface contained more extensive hemorrhagic areas in the center.

Microscopic sections of these hemorrhagic lungs presented a type of pneumonia rarely met, except in fulminating cases at the height of an epidemic of pneumonia. It is rare probably because it is a stage much earlier than is seen at necropsies of pneumonia of pneumococcus origin, or of low grade pneumonias of other origin. The lesion is a rather irregular central or lobular alveolar hemorrhage with numerous distended air spaces scattered throughout the area (Fig. 2).

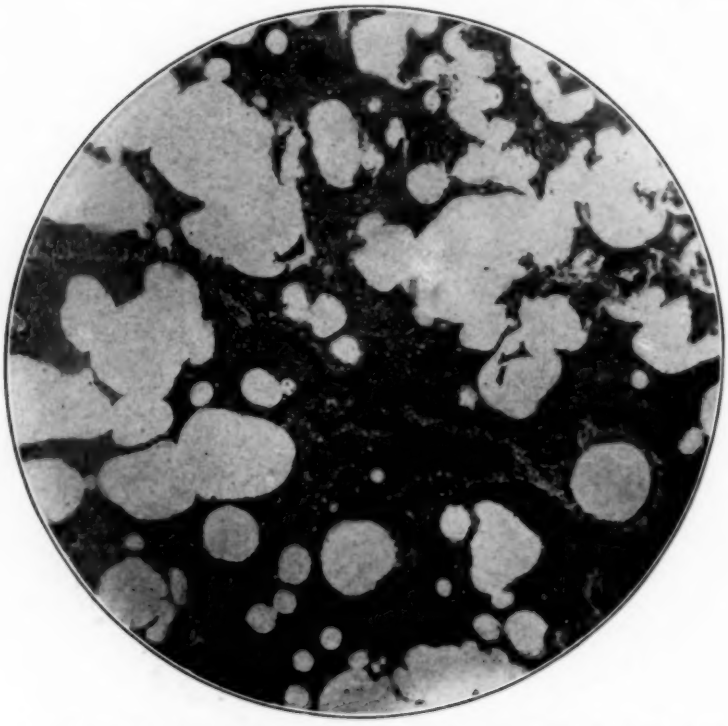

Fig. 2.—Microphotograph of a lung section from mouse 23, showing an emphysematous hemorrhagic type of pneumonia characteristic of the acute toxic stage of the epidemic.

Various stages of this were found. Some mice died at a very early period when no other lesion than an extreme capillary engorgement and serous alveolar exudation could be found, although usually in the central part of the lobes areas of alveolar hemorrhage were present.

The subsidence of the epidemic among the mice was prolonged and marked by a recrudescence of the acute toxic hemorrhagic form of the disease. Greater numbers of the sick mice began to have promi-

nent respiratory embarrassment and prolonged course. Such mice at necropsy presented a great variety of lesions in different lobes or even in the same lobe; purulent bronchitis in many stages of healing with obliteration of bronchi, limited or widespread polymorphonuclear alveolar exudate, lobular or fused areas of alveolar hemorrhage or simple capillary engorgement.

The infection among the guinea-pigs appeared later than among the mice and apparently took origin from the prevailing mouse epidemic at about the height of the latter. It is recalled that there were two rows of guinea-pig cages below the mice cages on one side of the animal room. The first infected guinea-pigs were noted in the row directly beneath the mice, and the infection was limited to the pigs of this side of the room for two weeks. The spread to the other side of the room dated from a general cleaning and sterilization of the cages, isolation of all sick pigs and transfer of all healthy appearing pigs to common outdoor pens or to cleaned cages on the uninfected side of the room. This attempt to rid the animal room of all infected cages only served to spread the disease. This was understood later when it was found by many necropsies and cultures that in an infected stock many apparently normal pigs show some lung lesion and give positive cultures of the *Bacillus bronchisepticus* from the trachea in more than 50 per cent.

PROTOCOLS

The symptoms of the first guinea-pig affected were those of a very severe primary toxic reaction with early appearance of marked respiratory embarrassment. The following is the protocol:

Pig 21: *History.*—A 300 gm. animal in a cage with six other pigs, directly beneath infected mice cages.

April 4, 1919: Breathing rather rapidly, with occasional pause and expiratory grunt; inactive; fur roughened; evidently sick.

April 5: At 2 p. m., respirations 200 per minute, labored, almost constant expiratory grunt; occasional cough; pig inactive. Leukocyte count, 11,300; polymorphonuclears, 65 per cent.; mononuclears, 35 per cent.; temperature, 101.8 F. At 6 p. m., respirations 180. At 12 p. m., pig appeared somewhat better, respirations still rapid and labored, however.

April 6: At 3:30 a. m., and at 7 a. m., condition unchanged; still quite rapid respirations with grunting expiration, inactive, fur roughened, but not appearing quite so sick as on previous day. At 1:30 p. m., respirations 170; temperature 100.4 F., evidently improving. At 3 p. m., killed by blow on back of head.

Necropsy.—There was a slight increase of peritoneal fluid; serous surfaces smooth and glistening; no evident pathology in abdomen. The medial, ventral and cephalic lobes of the left lung appeared completely involved in a firm lobular gray consolidation. A similar type of involvement was present in the same lobes on the right side but chiefly central in the cephalic lobe. Both caudal lobes were large, soft and crepitant, appearing normal, except for

moderate emphysema. The cut surface of these lobes, however, disclosed a few small gray areas near the hilus along the main bronchi, and a few punctate hemorrhages in the remainder of the lobe.

Microscopic: Sections revealed a fairly uniform type of pathology with varying degrees of involvement. The gray nodules seen in gross were areas of dense polymorphonuclear alveolar exudate, localized very definitely in the alveoli surrounding terminal bronchioles (Fig. 3). This lesion apparently began at the point of transition of the cuboidal epithelium of the terminal bronchiole to the flat epithelium lining the alveoli of the infundibulum. The infundibulum and surrounding alveoli are seen packed with polymorphonuclears

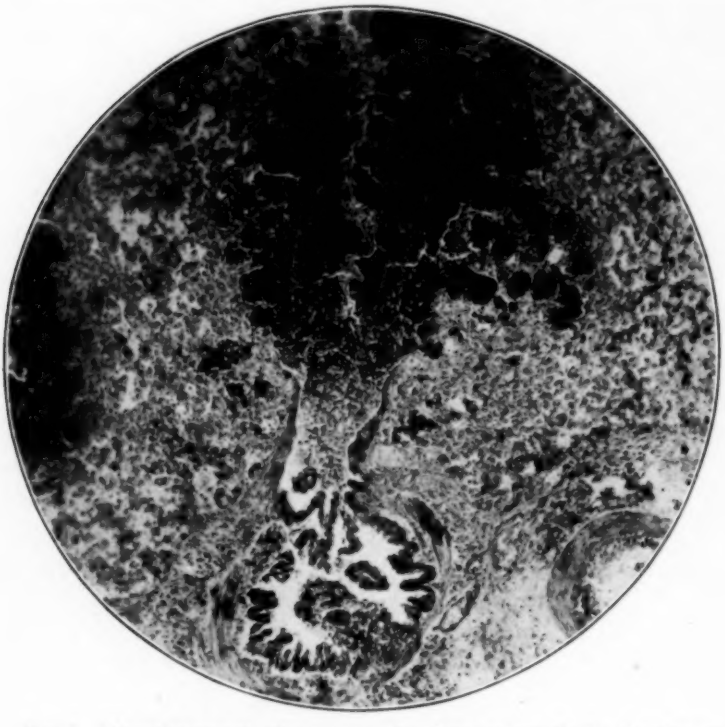

Fig. 3.—Microphotograph of a lung section from guinea-pig 21, showing an advanced infundibular lesion. This consists of an area of dense polymorphonuclear alveolar exudate subtended by a terminal bronchiole. The active process is distinctly delimited by the line of transition from the cuboidal epithelium of the terminal bronchiole to the flat epithelium of the infundibulum. There is no reaction about the bronchus except the general atelectasis and consequent slight cellular infiltration. The bronchial lumen contains only degenerated leukocytes which appear to have drained from the infundibulum.

which have not extended in great numbers into the bronchus but which evidently have blocked the terminal bronchiole. The alveoli beyond this rather sharply localized polymorphonuclear reaction are atelectatic, having a narrowed lumen, enlarged epithelial cells and a content of granular material with a few

large mononuclear cells. The small focal hemorrhages seen in gross section of the caudal lobes are identified as similarly localized areas of infundibular and surrounding alveolar hemorrhage, with blocking of the terminal bronchiole and inclusion of air bubbles in the hemorrhagic exudate. The best examples of this are found surrounding terminal bronchioles near the main bronchus of the lobe, indicating that the progress of the infection is by direct continuity of the bronchial mucosa, the later infection in the caudal lobes probably being controlled to some extent by gravity and distance.

Bacteriologic: A heavy growth of the *Bacillus bronchisepticus* was obtained from the trachea and the left cephalic lobe of the lung. Cultures from the heart's blood, peritoneum, pericardium and right caudal lobe of lung were negative. No other micro-organisms were present.

The following day, April 7, another guinea-pig on the same side of the room was isolated on account of ill defined symptoms of illness. The respirations were not increased, were quite shallow and only slightly irregular. This pig was under constant observation during the afternoon and there was some question from the symptoms whether he was sick or not. Unfortunately, he was killed late that night and no tissues were saved. The gross description of the organs at necropsy, however, gave a diffuse emphysematous hemorrhagic lesion in all lobes of the lungs as the only evident pathology. Cultures were not made.

April 8, a pig was found dead in a cage beneath the mice cages. This cage had been inspected on the previous day and this pig had not been identified as sick, although most careful observations were being made at this time. The protocol follows:

Pig 22: *History.*—April 8, 1919, found dead, evidently only a short time postmortem. Blood tinged froth was seen in the nostrils.

Necropsy.—Abdomen negative, except moderate vascular injection of viscera. The lungs were voluminous, not collapsing on opening the thorax, and there was an increased amount of clear fluid in both pleural cavities. The left cephalic lobe was mottled with dark red, chiefly central, and pink emphysematous areas, chiefly peripheral. The ventral lobe was a dark red color throughout and more firm. The left caudal lobe was more nearly normal but voluminous and contained scattered small focal areas of apparent hemorrhage. The lobes of the right lung were similar but less involved.

Microscopic: The predominant lesion in all lobes was a marked capillary engorgement with variable serous exudation in the alveoli. The central or hilus portions of the lobes gave evidence of a more severe capillary lesion. In many places there was thrombosis of the capillaries with evident degeneration of the alveolar septums, desquamation of the epithelial cells, beginning infiltration with polymorphonuclear leukocytes and serous exudation into the alveoli (Fig. 4). Alveolar hemorrhage was not prominent. The localization of these areas of most severe involvement did not throw much light on their manner of origin, whether in relation to bronchi or bloodvessels. There was an extreme edema of the perivascular tissue surrounding the larger blood vessels. The bronchi contained an eosin staining coarse granular material. The terminal bronchioles did not show a greater reaction than other regions and did not appear to be blocked by exudate.

Bacteriologic: Lung cultures gave a heavy pure growth of the *Bacillus bronchisepticus*. Sections stained for bacteria with Giemsa's stain demonstrated large numbers of small bacilli in the bronchi and in the more involved regions. In the bronchi they were located along the epithelial border but could

not be found, except rarely, in the bronchial wall. Immediately surrounding the larger bronchi they were especially abundant in the alveoli and the alveolar walls. There appeared to be a similar concentration about the larger veins. The areas of capillary thrombosis always contained many bacilli, not in the thrombosed capillaries but in clumps or within cells in the alveoli or in the alveolar walls in regions of degeneration.

It was at about this time that an attempt was made to check the epidemic by rigid isolation of sick pigs and sterilization of cages,

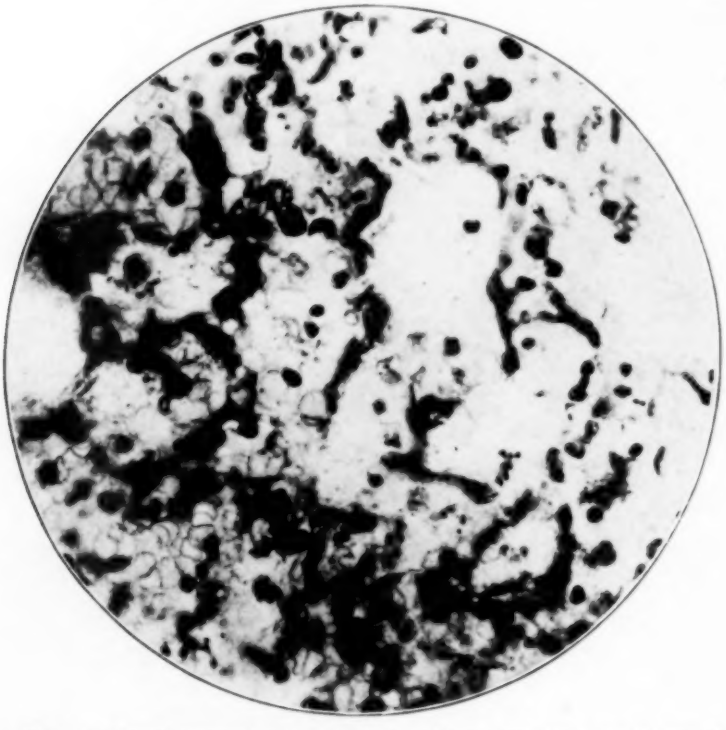

Fig. 4.—Microphotograph of an area of capillary thrombosis in the lung of guinea-pig 22. The thrombi are indicated by the irregular branching darkly stained areas. There is considerable necrosis of the alveolar walls, serous exudation and beginning polymorphonuclear infiltration. Capillary engorgement and hemorrhage are evident at the left side.

with transfer of some of the normal appearing pigs to common outside pens. But pigs continued to become sick, now in the outside pens and on the other side of the animal room. The following protocol is that af a breeding female from the outside pen and illustrates a pneumococcus complication:

PIG 25: *History.*—April 12, 1919, noted inactive and not feeding. That night a miscarriage occurred. The respirations increased moderately during the next two days, the pig becoming gaunt and weak. Killed April 15.

Necropsy.—There was found a massive gray lobular consolidation of both cephalic lobes and a more uniform darker consolidation of the ventral and median lobes. The caudal lobes were emphysematous, did not collapse and presented only small nodules along the main bronchi.

Microscopic: Sections presented a type of pathology somewhat different from that previously found. The predominant lesion was a rather widespread polymorphonuclear alveolar exudate, distinctly lobular in its distribution, yet confluent in many places. Very little fibrin was present, although places were found in which there was the typical fibrinopurulent alveolar exudate of pneumococcus pathology. The most characteristic lesion found in this and other pigs with a secondary pneumococcus infection was focal necrosis of variable size and shape.

Bacteriologic: Lung cultures from the ventral lobes gave a pure growth of the *Bacillus bronchisepticus*. A pneumococcus, tested by inulin fermentation and bile solubility, was recovered from the left median lobe.

The following protocol represents an infection in a newly received group of guinea-pigs, another instance of which is Pig 40. There seemed to be a tendency for acute cases to occur in new stock a few days after their receipt.

PIG 26: *History.*—April 15, noted somewhat inactive, yet of questionable illness. The following morning he was distinctly ill, with roughened fur, rather deep but not increased respirations, and noted occasionally coughing and rubbing his nose. At 5 p. m. April 16, respirations were 100 per minute; temperature, 101.6 F.; leukocyte count, 8,500; polymorphonuclears, 66 per cent.; mononuclears, 34 per cent. He was killed at this time.

Necropsy.—The abdominal organs appeared to be congested, the liver and spleen being a dark red color. On opening the thorax, there was not a very evident lung lesion from the ventral surface. Complete examination, however, showed the greater part of the median and ventral lobes involved by a grayish pink lobular consolidation. Similar lesions were found along the main bronchi in the cephalic and caudal lobes, reaching the surface in very few places.

Microscopic: The lesion in the lungs consisted of a lobular polymorphonuclear alveolar exudate, in places becoming confluent. Small polymorphonuclear lesions at terminal bronchioles, similar to those described for Pig 21, were found in less involved regions. The bronchi contained considerable mucus with a few polymorphonuclear cells. The bronchial epithelium appeared normal. A few small areas of focal necrosis were found in the alveolar lesions, similar to those of Pig 25.

Bacteriologic: Lung cultures from the cephalic lobes gave numerous colonies of *Bacillus bronchisepticus* and a few pneumococcus colonies. Heart's blood cultures were negative.

The following protocol of Pig 27 has seemed to have special significance in the interpretation of the pathology of epidemic pneumonia, as it was an acute toxic case at the height of an animal epidemic, killed at a very early stage and thus demonstrates the primary type of reaction at the onset of toxic symptoms.

Pig 27: *History.*—April 18, 1919. The symptoms of illness first observed at noon were ill defined, a slight inactiveness and indisposition and a watery appearance of the eyes. The respirations were not increased, were quite shallow and apparently normal. The fur was not roughened. It was a very questionable illness. At 3 p. m. the symptoms were more distinct. The pig remained very quiet and the respirations were distinctly abnormal. They were of the short gasping type, not rapid, varying greatly at different times, between 80 and 150 per minute, but more often below 100. There were occasional attacks of severe coughing during which the pig appeared to have great difficulty in breathing, as though suffocating. Between attacks shivering was noted. The temperature was 99.8 F.; leukocyte count, 2,100 per c.cm.; polymorphonuclears, 10 per cent.; mononuclears, 85 per cent.; transitionals, 5 per cent. At this time the pig was killed by a blow on the back of the head. (Note: This method of killing was selected on account of not wishing to enter the factor of a respiratory anesthetic. It, however, does leave the possibility of nasal or pharyngeal hemorrhage which may be aspirated into the larger bronchi. Consequently, such hemorrhage found in the larger bronchi must be disregarded as a possible artefact. A better choice of means of killing might have been made. It is hardly possible that this would confuse in the interpretation of terminal bronchiolar and alveolar lesions since such a death means an immediate cessation of respirations.)

Necropsy.—In both cephalic and ventral lobes there was a grayish, lobular, semitranslucent consolidation along the main bronchi, reaching the surface in only a few places. The remaining peripheral part of these lobes was emphysematous or normal appearing. The medial lobes were completely involved in a fairly uniform gray consolidation. Both caudal lobes presented on the surface and cut section many small punctate hemorrhages, hardly noticeable as abnormal. These lobes were large and did not collapse. Figure 5 is a photograph of a section of the right caudal lobe, passing parallel to the main bronchus, and illustrates very well the above description. The dense hemorrhage in the main bronchus must be disregarded as a possible artefact.

Microscopic: Sections of the gray lobular consolidation along the main bronchi of the cephalic and ventral lobes showed this to be a rather diffuse polymorphonuclear alveolar exudate, yet preserving evidence of its primary localization in the terminal bronchioles, by the denser exudate in these regions and a partial atelectasis of the intervening alveoli. The terminal and smaller bronchioles commonly appeared dilated with a dense polymorphonuclear exudate. The widely spread small punctate hemorrhages of the large caudal lobes were found to be small areas of infundibular hemorrhage. The bronchus and terminal bronchioles leading to each of these areas were normal appearing, except for a distinct indication of a hyperactive secretion of mucus by the bronchial mucosa with numerous globules in the lumen and some darkly staining granules which could not with certainty be identified as bacteria. The hemorrhagic lesions, when seen at selected places cut parallel to a terminal bronchiole (Fig. 6), or followed in serial sections, were constantly found to begin at the site of transition of the columnar or cuboidal epithelium of the terminal bronchiole into the flat epithelium of the infundibular alveoli, and extend in triangular or treelike manner from this stem. This hemorrhage apparently effectually blocked the terminal bronchiole, extending a variable distance into it. The only other type of lesion in these caudal lobes was a replacement of the focal infundibular hemorrhages by polymorphonuclear cells, this occurring more frequenty in the left caudal lobe near the hilus, indicating a slightly older process in this region. Areas with partial replacement by polymorphonuclear cells were found, this taking place first in the immediate region of the terminal bronchiole and later in the periphery of the hemorrhagic lesion.

Bacteriologic: Lung cultures from both cephalic and caudal lobes gave abundant pure growth of the *Bacillus bronchisepticus.* Heart's blood cultures were negative.

Guinea-pig 27 furnished very good material for the study of the mode of infection in this epidemic of pneumonia, since the caudal lobes presented widely distributed focal infundibular hemorrhagic lesions, representing a very early stage, and in one region showed the transition of these hemorrhagic lesions to a polymorphonuclear

Fig. 5.—Microphotograph of a section of an entire caudal lung lobe of guinea-pig 27, showing the widespread infundibular hemorrhagic reaction during the early acute toxic stage of the pneumonia. Each small dark area represents an infundibular hemorrhage of the type illustrated by Figure 6. There is no other lesion in this lobe.

type. The bronchi in general were normal appearing, except that the lumen most commonly was flooded with red blood cells. In a few bronchi only mucus globules were found, or polymorphonuclear

leukocytes and mucus where the bronchus subtended a polymorphonuclear infundibular lesion.

Some indication of the mode of infection should be given by the location of the bacilli during the various stages of the primary focal lesion. For this study of bacteria in section Wolbach's modification of Giemsa's stain was found most useful.[4] The *B. bronchisepticus* in tissue growth is very small, comparable in size to the influenza bacillus. Previous writers have located the bacilli along the ciliated

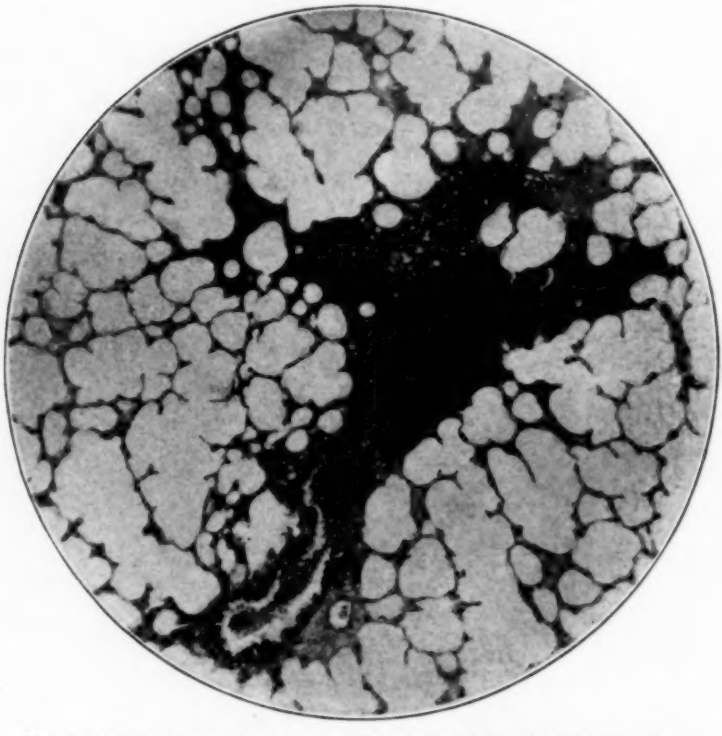

Fig. 6.—Microphotograph of a terminal bronchiole selected from the section illustrated by Figure 5, guinea-pig 27. The dark area consists of red blood cells, except that there are a few polymorphonuclear leukocytes in the immediate region of the terminal bronchiole and within the lumen.

border of the bronchial epithelium, but have not recognized the type of infundibular lesion presented by the entire caudal lobe of Pig 27, nor attempted correlation of the location of the bacilli with the stage of the infection.

4. Wolbach, S. B.: Studies on Rocky Mountain spotted fever, J. M. Res. **41**:1, 1919.

The pathologic evidence presented by Pig 27 indicates that the infection descended the bronchi without producing a manifest lesion until it reached the thin pavement epithelium of the infundibuli, where focal hemorrhages resulted which flooded the smaller bronchi. Search for bacteria in these bronchi revealed a considerable number of very small deeply staining granules at the epithelial border, partly free but frequently appearing to adhere to globules of mucus which were being actively extruded from the epithelium. The location of the greater number of these granules was at the tips of the folds of the mucosa. They could be traced into the terminal bronchioles

Fig. 7.—Microphotograph of bronchial mucosa from guinea-pig 27, to show the *Bacillus bronchisepticus* located between the folds of the mucosa. This area was selected from a small bronchus which subtended a polymorphonuclear infundibular lesion, similar to that illustrated by Figure 3. The bacilli are seen as small dots at the border of the epithelium.

and were found in the hemorrhagic exudates of the infundibuli. The identity of these granules is difficult to establish. The presence of the bacillus bronchisepticus in both caudal lobes was proven by culture, numerous colonies being obtained from a drop of lung juice withdrawn by capillary pipette through seared lung surface. The granules described were the only evidence of bacteria that could be found in relation to the earliest hemorrhagic infundibular lesion.

The *B. bronchisepticus* was easily and certainly found in bronchi which subtended polymorphonuclear lesions. These bronchi usually contained mucus globules and cell detritus of degenerated polymorphonuclear leukocytes which most probably had descended from the infundibular lesion, as there was no evidence of a peribronchial reaction or the passing of leukocytes through the bronchial epithelium. The bacilli were found chiefly in the depressions between the folds of the mucosa (Fig. 7). They were quite numerous in places and situated in contact with the ciliated border of the epithelial cells. Rarely could bacilli be identified in the central bronchial exudate or in the infundibular lesion. In the larger bronchi at the hilus the bacilli were more uniformly distributed along the epithelial surface. The location of the bacilli between the folds of the mucosa in the smaller bronchi may represent the persistence of the infection only in the more protected regions near the infundibular lesion.

The following protocols, given in brief, will indicate the course of events in succeeding days of the epidemic:

Pig 28: *History.*—April 18, 1919, an old breeding pig isolated on the preceding day on account of questionable illness. Leukocyte count, 10,700; polymorphonuclears, 66 per cent.; mononuclears, 34 per cent.; temperature, 101.6 F.; respirations 100 per minute. Killed by a blow on the head.

Necropsy.—Abdomen negative. Left cephalic lobe of the lungs completely involved by a gray type of consolidation. No hemorrhagic areas. Remaining lobes apparently normal except for marked anthracosis.

Microscopic: The involved lobe showed irregular areas of polymorphonuclear alveolar exudate, with intervening atelectasis or confluence of lesions. There also were areas of necrosis with abscess formation.

Bacteriologic: Cultures of the involved lobe gave a pneumococcus, pleural fluid and heart blood negative.

Pig 29: A young pig, weight 200 gm., found dead April 20.

Necropsy.—All lobes showed a dark red lobular involvement.

Microscopic: The lesion chiefly was that of capillary engorgement, centrally distributed with, in places, serous exudation or alveolar hemorrhage. One small bronchus was found dilated with polymorphonuclear cells and surrounded by polymorphonuclear alveolar exudate. Cultures from caudal lobes and trachea gave numerous colonies of the *B. bronchisepticus.*

Pig 30: *History.*—This pig was noted coughing April 20. He remained quiet but appeared active and irritable when disturbed. The respirations were not rapid, 100 per minute, but were of the short gasping type, irregular and interrupted by violent paroxysms of coughing as though suffocating. Shivering was noted. The temperature was 103 F.; leukocyte count, 14,000; polymorphonuclears, 23 per cent.; mononuclears, 77 per cent. He was killed by a blow on the head.

Necropsy.—The right cephalic, ventral and median lobes were completely involved in a moderately firm gray lobular consolidation. The right caudal lobe had a similar irregular area of gray consolidation at the hilus and along the main bronchus, but the remainder of the lobe was emphysematous and contained a few widely scattered punctate hemorrhages. All of the lobes of the left lung were emphysematous, did not collapse, and showed on the surface and cut section numerous small hemorrhagic spots, with no evident areas of gray involvement. The mucosa of the trachea and main bronchi was pale

and normal appearing. These did not contain blood but a blood clot was found in one of the first subdivisions of the left bronchus, subtending a small area of alveolar hemorrhage.

Microscopic: The gray lesions in the right lobes consisted of a dense polymorphonuclear infiltration in the infundibuli and surrounding alveoli, extending down into the dilated bronchioles. The intervening alveoli contained a few polymorphonuclear and mononuclear cells and appeared atelectatic. The peripheral part of the right caudal lobe and all lobes of the left lung, which showed rather uniformly distributed small hemorrhagic spots in gross, presented a type of lesion identical with that described in detail for the caudal lobes of Pig 27. These small hemorrhages were located in the infundibuli and the hemorrhagic exudate extended a variable distance down the bronchi. The mucosa of the bronchi was normal appearing except for evidence of active secretion of globules of mucus into the lumen. There was no dilatation of the bronchi or peribronchial reaction of any kind.

Bacteriologic: Cultures from the trachea and larger bronchi gave a heavy and pure growth of the *B. bronchisepticus*. Cultures from the blood cast in the left bronchus gave moderate numbers of the *B. bronchisepticus*. Culture from the right cephalic lobe of the lung gave a few colonies of the *B. bronchisepticus* and culture from a hemorrhagic area of the left lung was negative. Examination of Giemsa stained sections for the location of the *B. bronchisepticus* presented the same difficulties as in Pig 27. Numerous very small darkly stained granules were found near the folds of the mucosa, commonly adhering to globules of mucus, in the early hemorrhagic stage of the lesion. These could not positively be identified as bacteria. However, in the bronchi subtending the older polymorphonuclear lesions definite bacilli were found between the folds of the mucosa along the ciliated border of the cells.

Pig 31: Found dead April 21, several hours postmortem.

Necropsy.—The lungs were found diffusely hemorrhagic, with evident laking of blood and marked empysema. There were no areas of gray consolidation.

Microscopic: Marked postmortem degeneration with desquamation of the bronchial epithelium. There appeared to be a diffuse capillary engorgement with central alveolar hemorrhage or serous exudation. Focal lesions could not be identified.

Bacteriologic: Cultures were overgrown by a spore-bearing contaminant.

Pig 32: *History.*—Observed ill April 28; respirations, 125 per minute, irregular and deep Pig quiet but active when disturbed. Leukocyte count, 15,500; polymorphonuclears, 10 per cent., mononuclears, 90 per cent. Killed by blow on head.

Necropsy.—There was a central lobular gray consolidation in all lobes with a few peripheral puncture hemorrages.

Microscopic: Material was lost in process of embedding.

Bacteriologic: *Bacillus bronchisepticus* recovered in pure culture from the right caudal and cephalic lobes.

Pig 33: *History.*—May 5, had been under observation two days on account of inactiveness and abnormal respirations, 114 per minute, irregular and deep; leukocyte count, 17,700; polymophonuclears, 73 per cent., mononuclears, 27 per cent. Killed by blow on head.

Necropsy.—The cephalic and ventral lobes on both sides showed a lobular grayish red consolidation. Both caudal lobes were emphysematous and congested but with no distinct pneumonic foci.

Microscopic: The lesion in the cephalic and ventral lobes was a rather diffuse lobular polymorphonuclear alveolar exudate, most dense in the region of terminal bronchioles. Intervening uninvolved alveoli were atelectatic. A purulent pleurisy was found in section, not noted in gross. The larger bronchi contained no pus but a considerable amount of mucus. There was evidence of a

previous healed infection in the lung, presented by dense accumulation of lymphoid cells rather widely distributed and having a relation either to blood vessels or obliteraed bronchi.

Bacteriologic: Lung cultures gave the *B. bronchisepticus*, heart blood culture negative.

Pig 40: *History.*—May 23, 1919, found dead, not noted ill on previous day, although cage was examined for sick pigs. He was one of twelve pigs that had been received a few days previously from outside stock. The entire lot had been kept separate in clean cages.

Necropsy.—The lungs were very red and emphysematous. More extensive involvement in the central part of the lobes. The cut surface exuded blood stained fluid and air bubbles. No gray areas found.

Microscopic: Sections showed chiefly capillary engorgement, with serous or hemorrhagic alveolar exudate in the central region of the lobes.

Bacteriologic: Tracheal culture positive for the *B. bronchisepticus*, lung cultures negative.

Pig 48: This pig was a normal animal, killed May 17, and a lesion was found in the lungs which probably represents the final result in the healing of the focal infundibular lesions. Nothing was noted in gross but microscopic section revealed small foci of lymphoid cells distributed throughout the caudal lobes of the lung. These had no very constant relation to bronchi or blood vessels but occasionally were seen to be located at the termination of a bronchiole. Similar lesions were noted in Pig 33.

Pig 50: This pig was one which had gone through the epidemic without having developed evident illness. He was killed May 28, 1919. The lungs in gross appeared normal, except that the main bronchi appeared quite prominent in section. Microscopically these larger bronchi were found with a moderate peribronchial infiltration of lymphoid cells, a hyperplastic mucosa and an irregular lumen, evidence of a previous chronic bronchial infection with dilatation. Tracheal cultures gave a heavy growth of the bacillus bronchisepticus. Lung and heart blood cultures negative.

BACTERIOLOGY

This epidemic of pneumonia in mice and guinea-pigs was studied chiefly from the standpoint of pathology, hence the bacteriologic data add little toward the establishment of the etiologic micro-organism of the disease. However, the *B. bronchisepticus* was recovered sufficiently often from the trachea and lungs to indicate that we were dealing with the same type of epidemic disease interpreted by other investigators to be caused by this bacillus.

The first identification of this micro-organism in relation to this epidemic was in a mouse with the symptoms and pathology of purulent bronchitis. The infection among the mice had been noted several weeks previously but bacteriologic or pathologic observations were not made. The *B. bronchisepticus* in this and subsequent cases was identified by morphologic and cultural characteristics. The primary growth on blood agar plates was much less during the first twenty-four hours than at the end of forty-eight hours or in a twenty-four-hour subculture. The larger colonies were a grayish white color and emulsified readily in salt solution. Smears from the primary

growth revealed a very small gram-negative bacillus, somewhat comparable to the influenza bacillus in size and morphology. In subcultures the size was considerably larger. These bacilli were actively motile in bouillon culture and gave a diffuse clouding. They grew readily on ordinary media. They did not ferment dextrose, lactose, galactose, saccharose, maltose, mannite, dextrin or inulin in Hiss' serum water media. They were distinctly aerobic and on potato slants gave a rich yellowish brown growth within forty-eight hours. All of these qualities are in agreement with the micro-organism described by Ferry,[2] McGowan,[5] Torry[6] and Smith[7] as the etiologic factor in common epidemics of distemper and pneumonia in laboratory animals and called the *Bacillus bronchisepticus*.

TABLE 1.—EPIDEMIC PNEUMONIA IN MICE. NECROPSIES.

Date	Number	Bacillus bronchi-septicus	Type of Pneumonia
3/27/19	1	+	Purulent bronchitis
4/ 9/19	2	—	Purulent bronchitis
4/ 9/19	3	+	Purulent bronchitis and lobular
4/ 9/19	4	—	Purulent bronchitis
4/11/19	5	+	Purulent bronchitis, lobar and hemorrhagic
4/13/19	6	—	Lobular and hemorrhagic
4/13/19	7	—	Hemorrhagic
4/13/19	8	—	Purulent bronchitis and hemorrhagic
4/18/19	9	—	Hemorrhagic
4/18/19	10	—	Lobular and hemorrhagic
4/18/19	11	—	Lobular and hemorrhagic
4/18/19	12	+	Purulent bronchitis and hemorrhagic
4/18/19	13	—	Hemorrhagic
4/18/19	14	—	Hemorrhagic and lobular
4/24/19	15	—	Hemorrhagic and purulent bronchitis
4/24/19	16	—	Purulent bronchitis
4/27/19	17	—	Negative
4/27/19	18	—	Hemorrhagic
4/27/19	19	—	Hemorrhagic and purulent bronchitis
4/27/19	20	+	Hemorrhagic
6/ 1/19	21	—	Lobular, hemorrhagic and purulent bronchitis
6/ 1/19	22	—	Lobular, hemorrhagic and purulent bronchitis
6/ 1/19	23	—	Lobular, hemorrhagic and purulent bronchitis
6/ 1/19	24	+	Purulent bronchitis and hemorrhagic

Lung cultures were made from twenty-four mice submitted to necropsy during the epidemic, with recovery of the *B. bronchisepticus* in only six of these, or 25 per cent. (Table 1). Tracheal cultures were not made from the mice which may partly account for the low percentage of positive cultures, since it is recognized that lung cultures are commonly negative in this disease when taken from the hemorrhagic lesions or healing processes.[6]

5. McGowan, J. P.: A laboratory epidemic of distemper, J. Path. & Bacteriol. **15**:372, 1910.

6. Torrey, J. C., and Rahe, A. H.: Studies in canine distemper, J. M. Res. **17**:291, 1913.

7. Smith, Th.: Some bacteriologic and environmental factors in the pneumonias of lower animals, with special reference to the guinea-pig, J. M. Res., **24**:291, 1914.

The *B. bronchisepticus* was recovered more constantly from the guinea-pigs (Table 2). Fifteen pigs which developed symptoms of the epidemic disease were submitted to necropsy. Lung or tracheal cultures were made in fourteen of these, with recovery of the *B. bronchisepticus* in twelve. Of the two negative cultures, one contained only a pneumococcus and the other was overgrown by a spore bearing bacillus. The pneumococcus was recovered in three cases, each time from lung culture and in one of which there was a pneumococcus peritonitis.

TABLE 2.—Epidemic Pneumonia in Guinea-Pigs. Necropsies.

Date	No.	Bacillus bronchisepticus		Pneumococcus		Type of Pneumonia
		Tr.	L.	Tr.	L	
4/ 6/19	21	+	+	—	—	Polymorphonuclear and hemorrhagic infundibular pneumonitis
4/ 7/19	..	..	..	..	..	Hemorrhagic
4/ 8/19	22	.	+	..	—	Serohemorrhagic
4/15/19	25	..	+	..	+	Lobular with necrosis
4/16/19	26	..	+	..	+	Infundibular, lobular, necrosis
4/18/19	27	..	+	..	—	Infundibular and lobular
4/18/19	28	..	—	..	+	Lobular with necrosis
4/20/19	29	+	—	—	—	Serohemorrhagic
4/20/19	30	+	+	—	—	Infundibular and lobular
4/21/19	31	..	..	..	..	Serohemorrhagic
4/28/19	32	..	+	..	—	Lobular
5/ 5/19	33	+	..	—	..	Lobular and healed infundibular
5/ 5/19	34	+	.	—	..	Lobular
5/13/19	35	+	..	—	..	Serohemorrhagic and lobular
5/23/19	40	+	..	—	..	Serohemorrhagic

Twenty apparently normal pigs were killed during the subsidence of the epidemic. Tracheal or lung cultures in these gave the *B. bronchisepticus* in eleven cases, frequently in abundant pure culture. A Type II pneumococcus was recovered from one pig.

The location of the bacilli in the tissues studied in microscopic section has been presented in detail in connection with the protocols, especially that of Pig 27.

DISCUSSION

The observations in this epidemic of pneumonia present two subjects for discussion. The first is the interpretation of the course and pathology, strictly confined to the animal epidemic. The other is the significance of these observations in the interpretation of human epidemics of pneumonia.

In this animal epidemic the infection apparently began as nasal infection or distemper among mice which were in very crowded quarters. Later it became transformed into a predominantly bronchial infection which in the more severe cases presented the symptoms and pathology of purulent bronchitis. The next step in the course of the epidemic was a change to a fulminating toxic pnemonia with

very few respiratory symptoms and an emphysematous serohemorrhagic lung lesion. The subsidence was marked by a return of the predominant respiratory symptoms, but greatly varied lesions were found in the lungs, even of single animals, representing all stages from irregular areas of hemorrhage or polymorphonuclear exudate to purulent bronchitis or lobes with old obliterative bronchial lesions. The mortality rate was not very high among the mice and a large percentage probably became infected without being identified as ill. This was supported by almost invariably finding old lesions in the smaller lobes of supposedly normal mice killed late in the epidemic, and frequently finding active or even hemorrhagic lesions in mice that appeared quite well. A recurrent outbreak of the fulminating hemorrhagic pneumonia appeared in a few mice cages during the decline of the main epidemic, illustrating the possibility of a more virulent infection being superimposed on an existing or previous infection, as old lesions were found in conjunction with the hemorrhagic lesions in most of these mice.

The infection appeared among the guinea-pigs only after it had been prevalent among the mice several weeks. An environmental factor in the transmission of the infection is indicated by the fact that the first pigs affected were directly beneath the mice cages and the infection remained localized on this side of the animal room until an attempted cleaning spread normal appearing but evidently infected stock to other cages and pens. In the transmission of the infection from the mice to the guinea-pigs the stage of pneumonia appearing in the first pigs affected corresponded to that of the mice at that time. The distemper and the long period of chronic illness with marked respiratory embarrassment characteristic of purulent bronchitis did not occur in the pigs. The onset in the first pig affected was sudden and toxic.

The predominant lesion in this and several other pigs of the early nonfatal cases was a focal infundibular hemorrhage or polymorphonuclear exudate. This began at the point of transition from the cuboidal epithelium of the terminal bronchiole to the flat respiratory epithelium of the infundibulum. It extended a variable distance into the surrounding alveoli and appeared to dischargè into the terminal bronchiole, effectually blocking this in many instances.

The most interesting and most completely studied example of this type of pneumonia was Pig 27, killed at a very early stage when marked depression was evident. Both caudal lobes contained widely spread small infundibular hemorrhages. These focal hemorrhages would seem to represent the characteristic initial lesion of the early or milder cases at the beginning of the predominantly toxic stage of this epidemic of pneumonia. The location of this lesion, its evident

older stage in the smaller more dependent lobes or along the main bronchi, and the generally normal appearing bronchi, would indicate a descending bronchial surface infection resulting in a toxic inflammatory reaction only when it reaches the thin respiratory epithelium of the infundibuli and thus comes in intimate contact with the blood capillaries. The first reaction, when there is sufficiently extensive involvement to produce systemic effects, is that of a severe toxemia, chill, prostration, slow irregular respiration and leukopenia. The second reaction is a respiratory embarrassment, due to the blocking of a sufficient number of terminal bronchioles to give symptoms of suffocation. The replacement of the primary hemorrhagic exudate with polymorphonuclear leukocytes is accompanied by a moderate blood leukocytosis. It is significant that all of the pigs presenting the focal infundibular pathology were killed. Those which died after several days illness presented confluent or lobular areas of polymorphonuclear exudate and those which died during the night without having been identified as ill in the previous day presented a more diffuse capillary engorgement, serous exudation and hemorrhage.

The pathology of these rapidly fatal cases was radically different from the infundibular pneumonitis occurring at the same time. This consisted of a more diffuse capillary lesion, most marked in the central or hilus portions of the lobes. It varied from a simple engorgement with slight serous exudation to capillary thrombosis, necrosis of the alveolar walls and hemorrhage into the alveoli. The relation of the bacteria to the more severe lesions indicated a diffuse hilus invasion probably by lymphatic channels but not clearly indicated. Older stages of this same type of lesion in more protracted cases seemed to be represented by irregular confluent areas of polymorphonuclear exudate and necrotic areas with bordering polymorphonuclear infiltration, representative of the places of capillary thrombosis. The difference between this type of pathology and the focal infundibular type could be explained by the increase of virulence of the invading micro-organism until it is enabled to invade diffusely through the bronchial mucosa and spread by lymphatic channels.

The subsidence of the epidemic among the guinea-pigs gave a great variety of lung lesions, as was observed among the mice. Hemorrhagic lesions were superimposed on old obliterative lesions. In many apparently normal pigs killed after the epidemic had subsided old lung lesions were found, the commonest being numerous focal accumulations of lymphocytes throughout a lobe of the lung. These probably represented replacement of the focal infundibular polymorphonuclear lesions by mononuclear cells. A few cases were found with the characteristic lesion of healed purulent bronchitis.

The predominant micro-organism recovered in lung and tracheal cultures was the *Bacillus bronchisepticus*, most commonly in pure culture but in a few cases complicated by a pneumococcus. The bacilli could not positively be identified in sections of lung during the earliest stage of infundibular hemorrhagic reaction, but numerous small granules located on the folds of the bronchial mucosa and adhering to mucus globules suggest strongly their identity as bacteria.

These observations on the course and pathology of an animal epidemic of pneumonia seem to be of significance in the interpretation of human epidemics of pneumonia. The recent epidemic of streptococcus pneumonia in the Army corps is the one most completely studied and best understood in this country. This epidemic most probably took its origin from the prevalent streptococcus pharyngitis and bronchitis which preceded the more severe pneumonia.[8] The first stage of the epidemic of pneumonia was recognized and reported.[6] It was characterized by a fairly uniform type of pathology, that of purulent bronchitis, and had a common association with measles. As the virulence of the streptococcus increased a more diffuse lobular pneumonia occurred more frequently and finally true epidemics of streptococus pneumonia occurred without any relation to measles.[9] These epidemics developed rapidly, ran a course of six to eight weeks and the cases presented a predominantly toxic reaction with fulminating course and frequently a diffuse hemorrhagic lung lesion. During the subsidence of the epidemics a greater variety of pathology was encountered, with more cases of lobular pneumonia or interstitial bronchopneumonia as defined by MacCallum. Thus, if the entire course of the streptococcus infection is followed, it is found to have developed along a course very similar to the animal epidemic of pneumonia: from a prevalent mild pharyngeal and increasingly bronchial infection through a period of purulent bronchitis, to an independent epidemic of lobular and hemorrhagic pneumonia, with subsidence through somewhat similar stages in reverse order. This similarity with the course of events in the animal epidemic is significant of the life history of an epidemic of pneumonia.

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8. Cole, R.: Etiology and clinical features of the pneumonia occurring at a base hospital, J. A. M. A. **70**:1146 (April 20) 1918. Irons, E. E., and Marine, D.: Streptococcal infection following measles and other diseases, J. A. M. A. **70**:687 (March 9) 1918.

9. MacCallum, W. G.: Pathology of the epidemic streptococcal bronchopneumonia in the Army camps, J. A. M. A. **71**:704 (Aug. 31) 1918. Miller, J. L., and Lusk, F. B.: Epidemic of streptococcus pneumonia and empyema at Camp Dodge, Iowa, J. A. M. A. **71**:702 (Aug. 31) 1918. Lucke, B.: Postmortem findings in measles bronchopneumonia and other acute infections, J. A. M. A. **70**:2006 (June 29) 1918.

With this possible analogy in view it is most interesting to consider the pandemic of influenza and influenzal pneumonia in this light. The origin of the pandemic from all accounts seems to have been in Europe and most probably in the military camps, as the same environmental factors were present there as in the camps of this country where the epidemic of streptococcus pneumonia developed. A fact which immediately comes to the attention is that "there was prevalent during the late winter and early spring of 1916-1917, in the camps of northern France a severe type of bronchial infection, with a symptom complpex quite distinctive, very fatal, and which assumed such proportions by the end of January, 1917, as to constitute almost a small epidemic." [10] This disease presented the typical picture of purulent bronchitis and the predominant micro-organism recovered from the lungs and bronchial exudate was the influenza bacillus, with the pneumococcus playing an important secondary rôle and only a comparatively rare hemolytic streptococcus. The investigators [10] concluded that this disease was caused by the influenza bacillus and noted the fact that a mild influenza epidemic was actually in progress at that time.

This purulent bronchitis disappeared during the summer of 1917 but recurred during the winter of 1917-1918.[11] The chief problem during that winter, however, was a disease or diseases commonly called "P. U. O," (pyrexia of unknown origin), claimed by many to be a capillary bronchitis and suggestive of an atypical influenza.[12] Following this prevalence of "P. U. O." came in April and May, 1918, the first recognition of a widespread epidemic of influenza in the first and second English Armies in France.[13] In July the pandemic quality and increasing severity of the infection were evident,[14] it reaching this country the latter part of August with the well known severe toxic symptoms of onset and hemorrhagic pulmonary complications.[15] The preceding course of events suggests very strongly the gradual development of influenza in the camps of Europe through

10. Hammond, J. A. B., Rolland, W., and Shore, T. H. G.: Purulent bronchitis, Lancet **2**:41, 1917. Abrahams, A., Hallows, N. F., Eyre, J. W. H., and French, H.: Purulent bronchitis. Its influenzal and pneumococcal bacteriology, Lancet **2**:377, 1917.

11. McWalter, J. C.; The phenomena of purulent bronchitis, Brit. M. J. **1**:119, 1918. Eyre, J. W. H., and Lowe, C. E.: Prophylactic vaccination against catarrhal affections of the respiratory tract, Lancet **2**:485, 1918.

12. Pasteur, W., and Hudson, B.: A clinical contribution to the study of P. U. O., Lancet **1**:95, 1918. Annotation: Camp infections, Lancet **1**:810, 1918.

13. Influenzal Committee: The influenza epidemic in the British armies in France, 1918, Brit. M. J. **2**:505, 1918.

14. Maude, A.: Influenza and purulent bronchitis, Lancet **2**:324, 1918.

15. Keegan, J. J.: The prevailing pandemic of influenza, J. A. M. A. **71**: 1051 (Sept. 28) 1918.

a well defined stage of purulent bronchitis, a transition to the stage of infundibular pneumonitis (P. U. O.) and its final development into the stage of acute toxic hemorrhagic pneumonia.

This analogy might be extended further to include pneumococcus pneumonia, in which the well known pneumococcus bronchopneumonia of children would be representative of the developmental stage leading to the later acute toxic lobar pneumonia of young adults.

It is recognized that many features of epidemic pneumonia remain yet to be explained and established before acceptance should be given to the analogy presented in this paper. However, the recognition that epidemics have several stages in their development, each with certain distinctive features of symptomatology and pathology, should lead to a broader conception of epidemic diseases.

SUMMARY

1. This animal epidemic of pneumonia developed through the following stages, fairly well defined by symptoms and pathology:

(a) Nasopharyngeal infection (distemper).
(b) Mild bronchitis.
(c) Purulent bronchitis.
(d) Infundibular pneumonitis.
(e) Lobular pneumonia.
(f) Diffuse serohemorrhagic pneumonia.
(g) Subsidence in less distinct reverse order.

2. The epidemic of streptococcus pneumonia in the Army camps presented a somewhat similar course of events in its development.

3. The development of the pandemic of influenza can be traced in similar manner.

4. It is suggested that pneumococcus pneumonia should be considered in a similar course of development.

5. The recognition of purulent bronchitis as the natural precursor of an epidemic of acute toxic pneumonia places great significance on the prevalent influenza bacillus purulent bronchitis in the army camps of Europe during the winter of 1916-1917 and supports the view that the influenza bacillus is the cause of influenza.

REPORT OF A CASE OF HEMORRHAGIC SMALLPOX

A CONSIDERATION OF THE RÔLE PLAYED BY THE HEMOLYTIC STREPTOCOCCUS *

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The presence of the hemolytic streptococcus in the blood preceding and during the eruptive stage of a case of hemorrhagic smallpox led us to inquire whether this was a common finding in this form of smallpox. A search through the literature failed to give any information on this point. The close association of the streptococcus with variola is well known. In forty necropsies, practically all of which were in severe cases of smallpox, Perkins and Pay [1] found streptococci in the heart's blood and viscera of thirty-eight, or in 95 per cent. of the cases. Of these forty cases three were of the purpuric type, nine of the so-called secondary hemorrhagic type (variola hemorrhagica pustulosa), twenty-four of the confluent type, one discrete, two varioloid and one desiccating. The streptococcus was present in all of the cases except one purpuric and one varioloid case. These same workers examined the blood of twenty patients, before or just after death, and found streptococci present in eleven, or 55 per cent. If we consider only the sixteen more serious cases in this group, streptococci were present in 69 per cent.

Ewing [2] examined the blood after death in twenty-nine cases of smallpox and demonstrated the streptococcus in all. The abundance of the growth was found to be uniformly proportional to the severity of the disease, and in the primary hemorrhagic cases the cultures were remarkably profuse. In five cases cultures of the circulating blood were examined with a negative result. Only one of these cases was fatal. Ewing was greatly impressed by the early appearance and enormous development of the streptococcus infection in variola, especially in the primary hemorrhagic cases. It seemed to him that the smallpox virus "annihilates resistance" to the growth of the streptococcus.

Arnaud [3] found streptococci in the blood during life in two cases of hemorrhagic smallpox.

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1. J. M. Res., **10**:180, 1903.
2. Proc. New York Path. Soc., **1**:72, 1901-2.
3. Rev. de méd., p. 303, 1900.

Councilman [4] reported an intense streptococcus septicemia in all cases of hemorrhagic smallpox examined by him. No mention is made as to whether the organism was hemolytic or not. He regarded [5] the bacterial infection as more important in bringing about a fatal termination than the specific parasite.

Klein [6] refers to a statement by another English worker, Dr. Maurice, who asserted that in a large number of cases of hemorrhagic variola he found in the blood "septic organisms." From this he concluded that it is the entrance of such "septic microbes" into the blood which converts an ordinary case of smallpox into one of hemorrhagic smallpox. Klein believes this explanation is incorrect and argues that he has cultured the blood in a number of fatal cases of confluent smallpox and found a considerable variety of micro-organisms. He states that the organisms found in the blood of hemorrhagic smallpox do not differ from those found in the blood of confluent smallpox. Drs. Drysdale and Scholberg are quoted as having found in the majority of cases of fatal variola, *not hemorrhagic*, staphylococci and streptococci in cultures taken from the heart's blood. Klein concluded his report by citing eight cases of hemorrhagic smallpox in which blood cultures were taken. In only one of the cases was the culture taken during life; in this instance the blood was taken from the finger. No organisms were found. Cultures from the other seven cases were taken from the heart's blood post mortem, the elapse of time after death being as long as three days. Of these eight cases (including Nurse T and the Drysdale-Scholberg case) the cultures were negative in four and positive in four. He reported a variety of organisms; *Diplococcus pneumoniae*, *Streptococcus enteritidis*, *Streptococcus brevis*, and an organism which he termed *B. myxoides* because of the slimelike growth it produced on agar. The reliability of blood cultures taken several hours post mortem would seem open to question. In short, Klein drew the conclusion that the entrance of organisms into the blood stream was not the determining factor in hemorrhagic variola cases since half of his cases showed no organisms at all and the other half no constant organism. He considered the organism as a secondary invader, an expression of the patient's low resistance to infection.

The classification of hemorrhagic smallpox into the two types, purpura variolosa and variola hemorrhagica pustulosa, is dependent on the time of appearance of the hemorrhage in relation to the exanthem.

4. Modern Medicine. Osler-McCrae, 1913. Philadelphia, Lea and Febiger. **1**:805.

5. J. M. Res., **11**:358, 1904.

6. Thirtieth Annual Report of the Local Government Board, 1900-1901, London, p. 548.

In purpura variolosa the hemorrhage is primary, occurring before the exanthem, while in variola hemorrhagica pustulosa the hemorrhage is secondary and is not seen until after the variolous lesions have appeared, hemorrhage having taken place into the pustules. The case described here is one of purpura variolosa.

REPORT OF CASE

History.—The patient was a nurse, 21 years old. The family history was entirely negative. She had measles, chickenpox and whooping cough in early childhood, scarlet fever two years ago. Her first vaccination was done three months before the onset of the variola. This resulted in a very slight local reaction lasting only one or two days. Aside from frequent colds and "bilious attacks," she had always been well. For three days previous to the definite onset of the disease, the patient had noticed more or less headache and general malaise.

March 1, 1920.—First Day: Patient was suddenly taken ill with severe abdominal cramps, headache, backache and vomiting. The temperature was 102 F. There was a profuse discharge of blood from the vagina at this time, but this was not considered seriously, because the menstrual period was due. Within thirty-six hours, the uterine hemorrhage had greatly increased and there was bleeding from the rectum, mouth and nose. After pricking the finger for a leukocyte count it was noted that bleeding continued for several minutes. Blood appeared in the urine, the tongue became swollen and purple, and bright red blood was raised, apparently from the lungs. Blood culture taken at this time, which was before the appearance of any lesions suggesting variola, was reported as showing hemolytic streptococci.

March 3—Third Day: An erythematous rash was seen which extended over the face, arms, chest, and to a less extent over the lower extremities. This was later interpreted as a prodromal rash.

March 4.—Fourth Day: Hemorrhagic areas appeared on the chest, neck, back, and in both axillae, the largest extravasation being one on the right breast. This covered an area about the size of a dollar. At this time there was hemorrhage from all mucous surfaces, and she was raising rusty sputum. Following the application of external heat as treatment for a severe chill, a macular rash was observed on the forehead and arms. For the first time a diagnosis of variola was considered and the patient was transferred to the Contagious Hospital.[7]

March 5.—Fifth Day: Entrance Examination. Patient appears critically ill. She is exhausted and very uncomfortable. There is a very offensive odor. The face, arms and dorsal surfaces of the hands are covered with a confluent maculopapular rash, and it extends with less intensity over the chest and back. Numerous deep seated palmer and plantar lesions are seen. The papules are hard and shotty and all are in the same stage of development, except a few lesions on the face, which show beginning umbilication. Lesions are present in the mouth, those on the palate and pharynx standing out very prominently. On the right breast is a large purplish area, an extravasation of blood into the deeper tissues. This is well shown in Figure 1, which was made on the seventh day of the disease. Scattered over both arms are occasional small discolored areas varying in size from the diameter of a pea to that of a dime. There are also many petechial hemorrhages on both arms. Clots of blood cover the mucous membranes of the lips, mouth, nose and vagina. The face is greatly swollen and of a purplish hue. The eyes are almost shut, due to the confluent rash

7. We are indebted to Dr. J. A. W. Johnson of the Homeopathic Hospital for records and laboratory findings up to this time.

over the lids. Aside from an extremely rapid and weak pulse, the heart and lungs are negative. Abdomen negative, liver and spleen not enlarged. Although very ill, the patient's intellect is entirely clear. The urine is bright red with blood.

A provisional diagnosis of hemorrhagic smallpox with septicemia was made.[8] Blood culture showed hemolytic streptococci. With the hope of checking hemorrhage, 10 c.c. of horse serum was injected intramuscularly.

Fig. 1.—Seventh day of the disease. Showing beginning pustulation and hemorrhages into some of the lesions on the face and arms, as well as into the skin between the lesions. See notes of March 6 and 7.

March 6.—Sixth Day: Face still more swollen, eyes shut. The lesions stand out much more prominently, and many on the face, chest, and arms are black, due to hemorrhage into the lesion. Most of the lesions are in the vesicular stage. There is a striking increase in the number of petechial hemorrhages over the arms. Close examination shows these minute hemorrhages to be located

8. Diagnosis of hemorrhagic smallpox confirmed by Dr. Cowie and Dr. Wile.

between and entirely distinct from the pocks. Nausea is still a very prominent symptom. Somewhat less blood in the urine. Blood culture shows hemolytic streptococci.

March 7.—Seventh Day: Hemorrhage not so noticeable, only slight bleeding from the lips. The urine shows less blood. Lesions now all pustular. The hemorrhagic lesions on the face are very prominent. This seems to be the height of the eruption. Picture taken today.

March 8.—Eighth Day: No further hemorrhage noticed today. Lesions in pustular stage. Patient is in better spirits this morning. She takes food very well, and there has been no vomiting. Swelling of the face has definitely receded. No further hemorrhages or petechiae. Lesions in the pustular stage over the entire body. The eyes are still somewhat swollen. Urine is much clearer. Patient complains of severe pain in the right arm. Examination shows a tense swelling of the dorsal surface of the hand, extending half way to the elbow. It is not red, is not hot to the touch, and does not fluctuate.

TABLE 1.—LABORATORY FINDINGS

	Day—March, 1920											
	2	3	5	6	7	8	9	10	11	12	13	14
Urine												
Color	.....	.....	red	red	red	straw	red	amb.	amb.	straw	straw	straw
Reaction	.....	.....	acid	acid	neu.	neu.	neu.	neu.	neu.	neu.	neu.	neu.
Specific gravity	.....	.....	1.020	1.020	1.019	1.019	1.019	1.019	1.019	1.019	1.019	1.020
Albumin	.....	.....	2+	+	+	+	+	+	+	+	+	+*
Sugar	.....	.....	0	0	0	0	0	0	0	0	0	0
Erythrocytes	.....	.....	.....	.....	.....	.....	.....	—	—	—	—	—
Erythrocytes	.....	.....	4+	4+	2+	+	+	+	+	+	+	+
Casts	.....	.....	0	0	0	0	0	0	0	0	0	0
Blood												
Erythrocytes	.....	.....	4,600,000									
Leukocytes	18,000	20,700	26,800	20,000	16,000	15,000	.....	12,000	12,000	.....	7,000	
Hemoglobin	.....	.....	75%	.....	75%	.....	.....	60%				
Small lymphocytes	13%	20%	8%	6%								
Large lymphocytes	.....	.....	14%	19%								
Polymorphonuclear neutrophils	87%	74%	68%	64%								
Polymorphonuclear eosinophils	.....	.....	0.5%	1%								
Myelocytes	.....	.....	10%	10%								
Clotting time, Min.	.....	.....	12	.....	.....	.....	.....	.....	.....	10		
Blood sugar	.....	.....	.....	.....	.....	0.080‡	.....	.....				
Blood urea	.....	.....	.....	.....	.....	.....	.....	0.035g ‡				
Blood cultures	Hem. strep.	.....	Hem. strep.	.....	.....	.....	.....	.....	.....	.....	Hem. strep.	

* Lewis-Benedict Method.

‡ Van Slyke modification of Marshall method.

March 10.—Tenth Day: No new hemorrhages. The lesions are far advanced into the pustular stage. The urine approaches a normal color. Severe pain in the right arm.

March 11. Eleventh Day: Lesions show early crusting. No further hemorrhage. Swelling of the face has almost disappeared, the nares for the first time are patent. Right arm still very painful.

March 12.—Twelfth Day: Patient seems very bright this morning. The face has cleared up remarkably, but the lesions over the chest and arms are slow in crusting. Later in the day patient complained of a tightness in her chest. This evening examination shows diminished breath sounds, prolonged high pitched expiration, and moist râles in the right base posteriorly. A few moist râles also heard in the lower left base.

March 13.—Thirteenth Day: No marked change in the eruption, delayed crusting of the lesions over the hands and body. No further hemorrhage. There is a striking change in the patient for the worse. Respirations are increasing

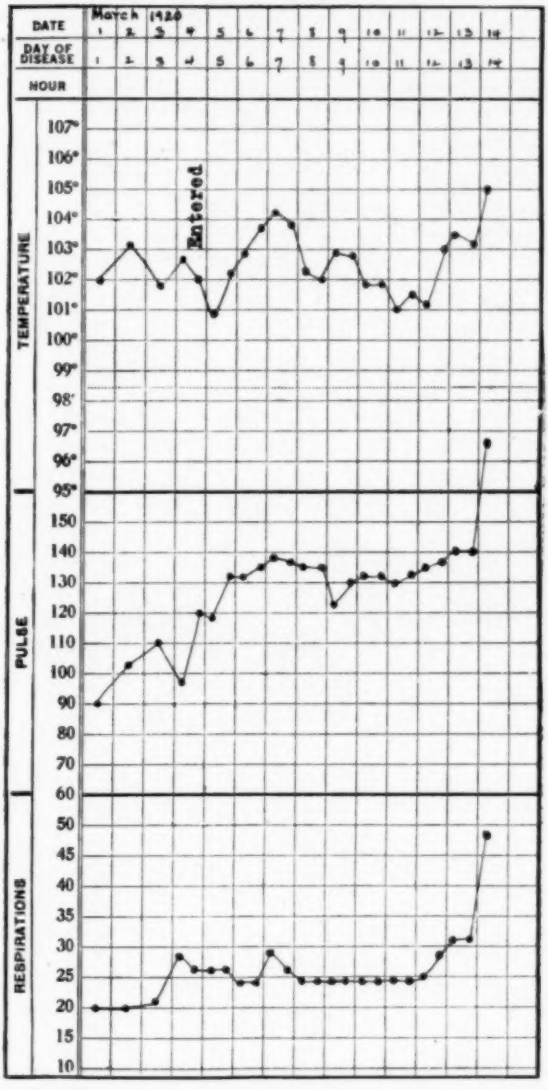

Fig. 2.—Clinical record of temperature, pulse and respiration from first to fourteenth day of disease.

The chest signs are now very distinct and extensive. Leukocytes have dropped from 12,000 to 7,000. The patient fully realizes that she is not so well. She remarks a great deal about her chest, how fast the respirations are, and of the tight feeling. Blood culture shows hemolytic streptococci.

March 14.—Fourteenth Day: No change in the lesions. There is no evidence of hemorrhage anywhere. The urine retains a good color. Condition this morning is extreme, respirations are labored, face and fingers cyanotic. Up to three or four hours before death, the patient's intellect was perfectly clear. She complained of severe pains in the head for which morphin was given. Permission to perform necropsy could not be obtained.

Blood Cultures.—Three c.c of blood was drawn from the median vein and placed in tubes containing 30 c.c. of plain beef broth. Hemolysis of the patient's blood was observed in these tubes in from twenty-four to forty hours. Microscopic examination showed a pure culture of streptococci, arranged in short chains. Rabbit blood agar plates showed isolated colonies with a well defined completely hemolyzed zone measuring from 2 to 3 mm. in diameter.

COMMENT

We have here presented a typical case of purpura variolosa in which the hemolytic streptococcus was present in the circulating blood as early as the first day of the disease. It is quite probable that it was present in the blood even before the onset symptoms. It apparently developed synchronously with the variola virus and continued throughout the course of the disease, a positive culture having been obtained on the thirteenth day.

In many diseases in which the hemolytic streptococcus is present, there is a tendency to the development of hemorrhage into the viscera, mucous membranes and skin. It will be of great interest to know if the streptococcus so frequently found in variola is of the hemolytic type or only of this type in the cases of hemorrhagic smallpox.

A noteworthy point in this case is the characteristic early appearance of the hemorrhages, the eruption developing and following the normal order through to the crusting stage on the eleventh to the fourteenth day. The case may be regarded as a combination of purpura variolosa and purpura hemorrhagica pustulosa, for as the lesions developed hemorrhage directly into many of them took place. It seems to be well illustrated that this patient conquered her smallpox in spite of the severe secondary infection, but succumbed to the latter when pneumonia, probably of the hemolytic streptococcic type, developed on the twelfth day of the disease.

This lends support to the opinion of Ewing, Councilman and Maurice that the streptococcus infection is of more importance in the fatal termination of variola than the variola virus itself.

RHEUMATIC MYOCARDITIS

A HISTOGENIC STUDY OF THE TYPE CELLS OF THE ASCHOFF BODY *

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BOULDER, COLO.

In view of the importance of this subject, comparatively little has been reported regarding the histogenesis of the typical cells of the rheumatic myocardial lesions first described by Aschoff.[1] On the other hand, many investigators have directed their attention to the etiology and specificity of the Aschoff body.

Most investigators [2] have agreed that the responsible organism is the *Streptococcus viridans* of Schotmüller, and that the lesions are specific for rheumatic fever. Thalheimer and Rothschild,[3] however, report finding typical Aschoff bodies in cases of chorea without rheumatic history. So far as we are aware their findings have not been confirmed, although the etiologic factor is said to be the same for both diseases.

Workers on the subject have either accepted Aschoff's original theory that the cells are "adventitial wandering cells," or they believe that these cells arise from the intramuscular connective tissue cells of the locality of the lesions. Aschoff (cited by MacCallum [4]) states that nowhere do the type cells arise from muscle cells, but the contrary is suggested by certain statements in the literature. For example, Coombs [5] says that when the cells are multinuclear the nuclei are arranged in the long axis of the cell and the cytoplasm is colored the same shade as muscle cells with Van Giesen's stain. Moreover, Geipel [6] notes that the nuclei of the muscle fibers, broken or eroded by the Aschoff body, or its etiologic agent, are subject to proliferation, the excess of nuclei collecting at the injured end. Structures observed in routine sections of heart muscle from the necropsy discussed in this paper raised the question whether it might not be possible to trace the origin of the characteristic cells in the Aschoff bodies with greater accuracy than has been done hitherto. Evidence which we regard

* From the Denison Memorial Research Laboratories of the University of Colorado.

1. Aschoff: Verhandl. d. deutsch. path. Gesellsch. **8**:46, 1904; Brit. M. J. **2**:1103, 1906.

2. Libman and Coller: Am. J. M. Sc. **111**:516, 1910. Wachter: München. med. Wchnschr. **55**:1101, 1908. Sternberg: Wien. klin. Wchnschr. **32**:522, 1919.

3. Thalheimer and Rothschild: J. Exper. Med. **19**:417, 1914.

4. MacCallum: Textbook of Pathology, 1916, p. 449.

5. Coombs: Brit. M. J. **2**:1513, 1907; Lancet **1**:1377, 1909.

6. Geipel: München. med. Wchnschr. **56**:2469, 1909.

as conclusive is presented herewith, to show that some of the cells, at least, represent degenerated muscle elements. Whether all the cells have the same origin remains an open question. Granted that the cells in question have more than one histogenetic origin, the divergent views of Aschoff, Coombs, Geipel, and others, are explained and correlated.

A brief description of a typical Aschoff body would not be amiss. The nodules are made up of large elements arranged more or less radially about a center, the cells being similar to but larger than the "epithelioid cells" of a tubercle, more nearly resembling the Sternberg

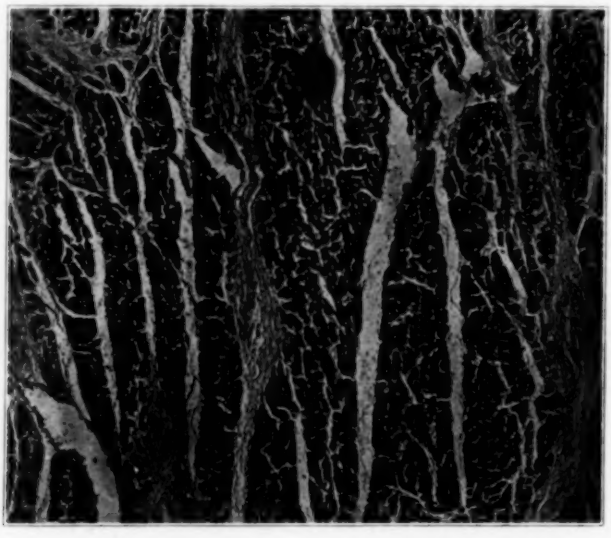

Fig. 1.—Low power field from left ventricle showing eight Aschoff nodules.

giant cells of Hodgkin's disease. The cells are often multinuclear, with rarely more than six or seven nuclei, and are round, fusiform, or an elongated oval shape. The Aschoff bodies are usually close to small vessels or capillaries and are surrounded by a more or less extensive zone containing chiefly neutrophilic with a few eosinophilic leukocytes, some plasma cells and small lymphocytes. All observers agree that the Aschoff elements are atypical cells, most theories placing them as developments from connective tissue cells under the influence of the toxins of the disease. As Huzella [7] says, "The elements of the myocardial rheumatic nodule are cells formed from the myocardial

7. Huzella: Virchows Arch. f. path. Anat. **213**:389, 1913.

connective tissue under the influence of the rheumatic virus, assuming very varying, irregular forms and then degenerating." It is our purpose to show that some, at least, of these cells are derived from muscle elements through degeneration or abortive attempts at regeneration.

The case that was used in the preparation of this paper affords favorable material for studying the histogenesis of these bodies because lesions of all stages were present in the heart.

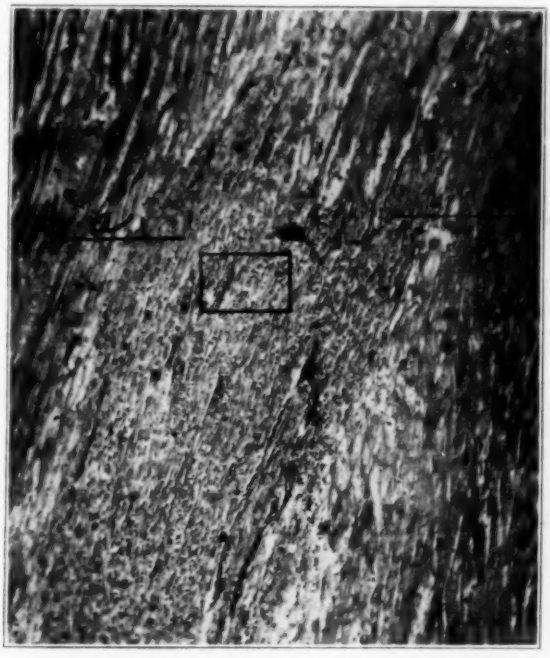

Fig. 2.—From papillary muscle, probably several confluent lesions. Area marked indicates field illustrated in Figure 8. Points indicated by letters referred to in text.

We are indebted to Dr. H. C. Dodge of Boulder for the privilege of studying the case.

REPORT OF CASE

J. F. S., aged 25, a former coal miner, was inducted into the army in June, 1918, and discharged in June, 1919. He claimed that he had never had rheumatism before he was taken into the army. While at Camp Cody he was troubled several times with rheumatism of the feet. After reaching France he suffered several attacks of tonsillitis and rheumatism, the latter, judging from the patient's account, apparently of an inflammatory character, and not confined

to his feet. He was discharged in "good physical condition." About Jan. 1, 1920, he had a severe attack of tonsillitis, and about January 20 a diagnosis of acute dilatation of the heart was made. This last was followed by an attack of acute articular rheumatism. These attacks recurring, he was placed in the University Hospital at Boulder March 1 and was kept under observation there until his death, April 29.

Clinical Course.—After a short period of seeming improvement, he underwent a series of attacks of acute rheumatism and complained of constant pain in the heart region. April 10 there was an attack of what seemed to be heart block with edema of the lungs, which soon cleared up. Attacks of the arthritis continued but seemed to be milder, and for a week previous to April 29 he was up in a wheel chair, being practically free from rheumatic pains. The day of his death there was a sharp attack of rheumatism accompanied by

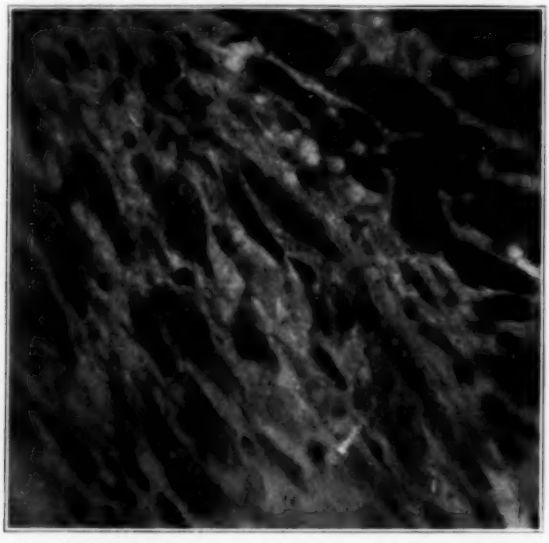

Fig. 3.—Field in a typical Aschoff body showing the epithelioid cells.

dyspnea, severe heart pains, orthopnea and pulmonary edema. The stethoscope revealed only two of the heart lesions found at necropsy, the mitral and the aortic.

ABSTRACT FROM THE NECROPSY PROTOCOL

The necropsy was held eighteen hours after death. There were no external signs except a very slight edema over the ankles. There were some fresh, easily separated adhesions over the left lung only. The lungs showed no areas of consolidation, but only slight crepitation, and on section and pressure yielded an abundant clear, frothy fluid. The heart was very large and the pericardium was closely and firmly adherent at all points. Mitral flaps were fused, thickened, rigid but not calcified, with a crescentic orifice and minute vegetations along the edge. The columnae carneae were shortened and fibrous. The aortic and tricuspid valves were similar to the mitral, while the pulmonary valve alone was normal. Left ventricle wall: 2 cm. thick; right ventricle wall: 12 (!) mm. thick.

Microscopic Examination.—The stains used were methylene-blue-eosin, methyl-green-pyronin, Mallory's iron-hematoxylin alone and in combination with eosin and with picric acid as counterstains. All illustrations were made from the iron-hematoxylin preparations as they showed the elements of the muscle cells the best. Regardless of the stain used, the cytoplasm of the type cells studied always stained the same shade and degree of intensity as did the cytoplasm of the muscle cells.

In every low power field there were from one to eight or ten nodules (Fig. 1) depending on the part of the ventricles examined. They were oftenest subendocardial and, as others have noted, it was found that, in order of the number of lesions, the papillary muscles come first, the left ventricle wall and the interventricular septum next, the right ventricular wall showing comparatively few lesions. Even with the low power it was plain that there were present lesions in all stages from the first sign of muscle cell necrosis with scarcely noticeable leukocytic infiltration to completely healed areas with quite dense scar tissue. The nodules, when recent, always were found around or near a

Fig. 4.—Late transitional stage from muscle to epithelioid cell. Inset is sketch of cell near center of picture.

small blood vessel, apparently, from its wall, an artery; or several such vessels may be found scattered here and there in a large nodule, possibly resulting from the confluence of several smaller ones.

DISCUSSION

The identification of the true Aschoff body was based on a study of its individual elements as demonstrated by the methylene-blue-eosin and the methyl-green-pyronin stains, and by its relation to the vessels. From the typical textbook types the lesions were traced back to the earliest demonstrable. In the present paper we shall confine our descriptions to the "large epithelioid cells," tracing them from the type found in the average Aschoff body through all stages to their earliest precursors.

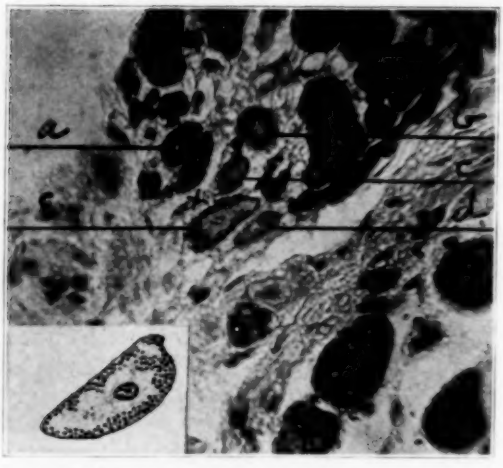

Fig. 5.—Early transitional stage from muscle to epithelioid cell. Inset is sketch of cell near center of picture.

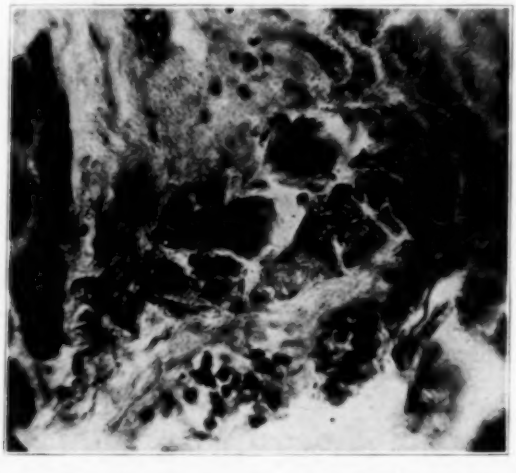

Fig. 6.—Separation of a muscle bundle into its components.

Figure 2 shows a field under higher magnification than in Figure 1, and cut in a different direction. This lesion is in a papillary muscle and at first was passed over as not being an Aschoff nodule. Closer study, however, revealed that it probably consists of several, at least four, confluent Aschoff bodies, a condition that, as far as we know, has not been reported before. The relation of the lesion to the muscle fibers is well shown, the latter seeming to break up and disappear in the lesion. At certain points (Fig. 2, a and b), the Aschoff cells are arranged in definite rows continuous with muscle fibers ending at the edge of the lesion as though the Aschoff cells originated by the fragmentation or attempts at regeneration of the muscle fibers.

In Figure 3 is shown the so-called "epithelioid cell" of the Aschoff body. There will be noted pear-shaped and elongated multinuclear cells with a fairly dark staining protoplasm. The cytoplasm is of even

Fig. 7.—Sketch of the central portion of Figure 6.

texture without more than the slightest suggestion of granules and no trace of fibrillae. The nuclei stain as a dark ring with a single dark nucleolus, in the center, target like, and number one to seven in each cell. These cells do not resemble fibroblasts, differing from them in their shape, size, reaction to stains, and number of nuclei. In the lesions studied there was usually ample opportunity to compare the two types of cells, since, when the lesion was at the stage exhibiting these cells, there were usually normal fibroblasts in good numbers in the same field with these abnormal cells.

Carrying the cell back through younger lesions we are able to show a clear series to the stage shown in Figure 4 where is seen a cell still showing evidences of being a muscle element. This cell has five nuclei and a rather large vacuole. The cytoplasm is colored the same as that of the cell discussed above and is otherwise identical with the epithelioid cell, except that there are a few striae at the poles of the cell consisting of small, deeply staining dots, a little larger and

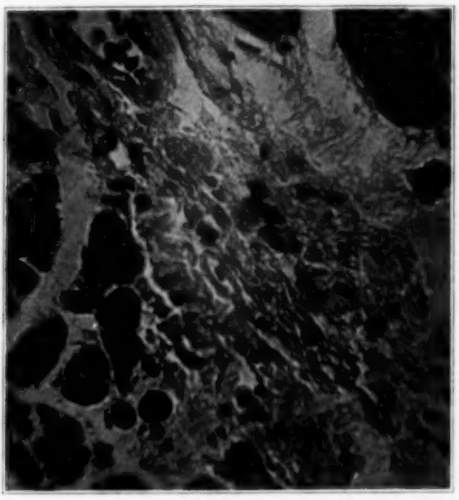

Fig. 8.—Healed lesion showing atypical muscle cells in the substance of the scar.

Fig. 9.—Transitional stage, long axis of the cell.

paler than those of normal muscle cells. The field used in the figure shows part of a rather young lesion.

It is but a few steps to the earlier stage shown in Figure 5. Each stage is well illustrated by many examples in many nodes. In this figure the photograph shows that the cell is a product of muscle cells. It clearly shows one nucleus in the center, the normal condition, and a border of striae represented by dots. That this cell is produced by separation of the cells of a muscle bundle into its constituent elements may be inferred from the appearance of such fields as shown in Figure 6, where a muscle bundle is shown in the process, but otherwise little changed from the normal, the striae being cut more obliquely than in Figure 5.

Fig. 10.—Sketch of the cell in the central part of Figure 9.

Referring again to Figure 5, the process by which the cell loses its striae is well illustrated. The cell marked *a* shows the earliest stage with the loss of only a few striae in the center of the cell, leaving a homogenous area. As shown in the other cells successively the process extends peripherally through the stage shown in Figure 4, where there are only a few striae at the cell poles with a decided proliferation of nuclei, to the stage illustrated in Figure 3.

It would be well to recall the way in which cardiac muscle cells acquire their fibrillae, since it is possible that the above mentioned cells should be regarded from another point of view. In the embryo the fibrillae appear first in the periphery of the cell and from there grow in toward the center. Therefore, it is possible that some of the cells studied may be the result of regeneration, rather than of degeneration. This is suggested by the statement of Geipel already quoted, and

by the appearance of such fields as are shown in Figure 8. This picture shows a healed Aschoff body in the center of which are several atypical but unmistakable muscle cells.

Not only do cross sections of the cells give a series from the "epithelioid type" to the unmistakable muscle cell, but the same is seen in sections depicting the long axis of the cell. Figure 9 shows under high magnification a rather large cell of a type intermediate between those of Figures 3 and 4. The cytoplasm takes the stains as preceding examples and contains a few rather indistinct fibrils, two of which clearly show cross striations and others give the suggestion of the presence of striae. As can be noted the cell is spindle shaped and about as wide as the adjacent nearly normal muscle cell. However,

Fig. 11.—Earlier transitional stage, long axis of the cell.

if it were not for the striae and the fact that some of the fibrillae seem to be continuous with those of more nearly normal muscle cells, one would hesitate to call the cell a muscle element. It is more like an Aschoff cell, and shows a clear resemblance to certain of the cells in such fields as illustrated in Figure 3. How such a cell arises is shown in Figure 11 by the cell with the two clear fibrillae, which show very clear cross striations. This cell was found lying deep in a nodule and very close to a vessel as is shown in the illustration, the dark wavy bands of connective tissue being from a vessel wall. The location, under low magnification, is indicated in Figure 2. Quite a number of such cells were found in various nodules studied.

Besides the typical Aschoff bodies, parts of which have been discussed above, there is present another type of lesion. These are areas of simple, early muscle-cell necrosis sometimes with early leuko-

cytic infiltration. Tracing one of these areas through serial sections, led to a small blood vessel occluded by an embolus, indicating that the area is an infarct in a quite early stage before the hemorrhagic zone was formed. Though we are unable to connect the oldest of these areas with the most recent of the identifiable Aschoff nodules because, perhaps, of the week's interval between the last two rheumatic attacks, mentioned in the case history, nevertheless, the idea presents itself that perhaps Aschoff nodules in their earliest stage, are very small infarcts.

We are not prepared to state that all of the "epithelioid cells" originate as above outlined, but it would seem from a careful study of such fields as have been depicted that many of the typical cells of typical Aschoff bodies are derived from muscle elements and that they have not been so described because of lack of such favorable material as was our good fortune to obtain. Further, it is our opinion that at least some of the Aschoff cells arise from muscle cells in two ways—through degeneration of existing elements and through regeneration. The bulk of the evidence points to the first of the two conclusions, but there is by no means little to make the second at least plausible. The case is exceptional. We do not know why such results could not be obtained experimentally, but an observation by Thalheimer and Rothschild [8] indicates that experimentally produced bodies are easily differentiated from true Aschoff bodies even when cultures from heart lesions are used.

CONCLUSIONS

1. At least some Aschoff cells are derived from muscle cells.
2. In most cases the cell is the result of degeneration and proliferation of the nuclei.
3. In certain cases the presence of striae at the periphery of the cell suggests the possibility that the cell is a product of purely regenerative activity.
4. Certain facts in our case suggest the further possibility that the process may begin as minute infarct.

8. Thalheimer and Rothschild: J. Exper. Med. **19**:429, 1914.

A STUDY OF THE LESIONS PRODUCED BY FILTRATES OF INFLUENZA SPUTUM *

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The hypothesis of a filtrable virus as the primary etiologic agent in epidemic influenza has been advanced by Nicolle and LeBailly,[1] von Angerer,[2] Bradford, Bashford and Wilson,[3] and by Gibson, Bowman and Connor.[4] The great diversity of bacteriologic findings in the disease would seem to render such a conception very attractive. It would appear very difficult to explain the epidemiologic characters of the disease on the assumption that it is primarily caused by any of the well known bacteria which have from time to time been associated with it, but which are also known to be present and active in the inter-epidemic periods. The clinical conception of influenza as a comparatively mild disease, characterized by a well marked toxemia and giving evidence of special predilection for the respiratory tract, and only dangerous, as a rule, when complicated by the so-called "secondary" pneumonia, from which a great variety of bacteria have been isolated, is also in harmony with the idea of an unknown primary cause. So, too, is the striking uniformity of the disease as observed in widely separated localities, irrespective of the fact that in one place one organism dominates the bacteriologic picture, and in another a totally different organism is found.

In spite of these elements of probability, the "filtrable virus" theory has not gained general acceptance, and the results of one group of investigators has been entirely discredited as far as their claims of cultivation of the organism are concerned.[5] The work of the men named, however, seems to confirm the claim that it is possible by the injection into experimental animals of filtrates of the sputum or blood of influenza patients to produce lesions of the lungs bearing some resemblance to those characterizing influenza, to cause the death of such animals occasionally, and to reproduce in other animals the same

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*From the Department Laboratory, Southern Department.

1. Nicolle, C. and LeBailly, C.: Compt. rend. Acad d. sc., **167**:607, 1918, and Ann. de l'Inst. Pasteur, **33**:395, 1919.

2. Von Angerer: München. med. Wchnschr., 1918, p. 1280.

3. Bradford, Bashford and Wilson: Quart. J. Med., **12**:88, 1918.

4. Gibson, H. G., Bowman, F. B., and Connor, J. I.: Brit. M. J., **2**:331, 1919; Spec. Rep. Med. Research Com. Brit. Nat. Health Ins., No. 36

5. Arkwright, J. A.: Brit. Med. J., **2**:233, 1919.

type of lesion by the further passage of filtered material. Whether or not the virus has been cultivated must for the present remain subjudice.

It occurred to me that light might be thrown on the subject by repeating the work in question with the idea of making a careful study of the lesions produced and comparing them with those accepted as characterizing the organs of patients dead of influenza. The return epidemic of January and February, 1920, at Fort Sam Houston, Texas, afforded an opportunity to obtain undoubted influenzal material and a series of experiments was inaugurated.

The general plan was to obtain a bacteriologically sterile filtrate of a sputum from an early severe case of influenza, to inject it into animals and to note results. Details of the technic employed will be given below. Results were considered positive only when the lungs of the infected animal showed microscopically a well marked lesion of the type subsequently described. The possibility that such lesions might be caused by a preformed toxin present in the patient's sputum has been borne in mind, and for this reason attention has been concentrated on the passage of the "virus" through a long series of animals rather than on the attempt to produce the lesions from a large number of cases of the disease.

Filtrates from the sputum in five cases of influenza have been used. In each instance positive results were obtained. In one case the gross lesion at necropsy was so slight that no further passage was attempted, although the microscopic findings were of a well marked and diffuse lesion of the same type as the others. A second strain was carried through two passages; a third through three passages with eight positive animals; a fourth through two passages with five positive animals; and a fifth through nine passages with twenty positive animals. In all, thirty-six animals, out of forty inoculated, have shown some degree of the process to be described; two were negative and two are still under observation.

The animals used have been rabbits, guinea-pigs and mice; inoculations were made intravenously, subcutaneously and in a few instances intraperitoneally. In each instance we have found the same type of lesion and all stages were noted. It is to be regretted that monkeys have not been available. Mice are, perhaps, the best animals for the purpose on account of convenience and the fact that it is oftener possible to give a lethal dose. This is probably not a matter of susceptibility but rather due to the fact that the dose employed is larger in proportion to the body weight. Owing to lack of space publication of detailed protocols of these experiments is impossible. An attempt will be made, however, to present the results with occasional references to especially interesting cases.

There has been no uniformity in the clinical symptoms observed after inoculation. Many animals have appeared to be in perfect health but when killed have shown marked lesions. When symptoms supervened, the period of incubation was extremely variable. In one rabbit (84 C) within twenty-four hours after inoculation the animal was extremely sick, refused food; its coat was rough; breathing was labored to such an extent as to suggest an obstructive condition in the air passages; temperature was elevated; death occurred in forty hours. Other rabbits showed no symptoms, except a slight loss of weight or in young animals a failure to gain as control animals of the same litter did. Temperature observations were negative in so many animals that they were discontinued later. Guinea-pigs showed no symptoms except a progressive loss of weight, in one case leading to the death of the animal after thirteen days. Mice were usually affected earlier. They showed a roughened coat, apathy and respiratory distress. The incubation period appears to be somewhat dependent on the effective dose administered, and there is at present no method of determining this factor.

The lesions found have varied greatly in degree but in kind they have shown prefect uniformity. The trachea has shown an inflammatory process characterized by hyperemia or hemorrhage in the intercartilaginous spaces so that the organ presented a marked "banded" appearance (Fig. 1). In many of the more severe cases the trachea and bronchi contained bloody froth or bloody mucus. The lungs did not collapse normally on removal from the thorax. There was in almost all cases some degree of dark red coloration on the surface of the lungs (Fig. 1). This varied in degree from the extreme represented by the rabbit mentioned that died in forty hours, in which practically the entire surface of the organ was a deep red color, to cases in which the only external sign was the presence of a few red spots a millimeter or two in diameter. In some instances the affected areas were sharply outlined, in others they were marked by a dusky red mottling with indistinct outlines. These doubtless represent different stages in the evolution of the process. Careful inspection of the surface of these lungs shows in most cases evidence of patches of emphysema. These are variously located, sometimes marginally, often between areas of the red coloration. Section of the affected organs shows in well marked cases the same general appearance as the surface. Areas dark red and denser than normal, usually sharply outlined from the lighter normal tissue, and areas of dilated vesicles are usually plainly to be seen. Portions cut from the dark areas float very low in water. In the more acute stages the cut surface is more moist than normal and may exude a bloody fluid or froth.

It has not been possible to show any relation of these lesions to the bronchi. With two exceptions the pleural surface has appeared unaltered. One of these was in a rabbit which showed a large empyema of the right side and a smaller accumulation of turbid fluid on the left side. The other was in a mouse infected with the filtrate of the lung of this animal which died after seventeen days and showed pleural adhesions and a small amount of a yellow fibrinous material in patches

Fig. 1.—Lung and trachea of rabbit 331. Tracheal banding, dark red spots and marginal emphysema are very evident.

over the right pleural surface. In both these animals the exudate was free from bacteria, as determined by careful examination of stained specimens and by culture.

The microscopic findings have been most uniform and characteristic. The lesion produced appears to begin as a marked hyperemia of the alveolar tissue of the lung. The lung in this stage looks as

if the capillaries had been injected, so plainly do they outline the walls of the air spaces. The alveoli are empty or contain large mononuclear cells and sometimes a few erythrocytes. This condition is not uniform throughout but occurs in irregularly distributed areas separated by normal tissue. Necrosis of the capillary walls, as evidenced by disappearance or fragmentation of the endothelial cells, is seen in some places. In more advanced cases the characteristic lesion of the condition is fully developed. This consists of hemorrhage into the walls of the alveoli with disappearance of the original capillaries. The resultant thickening of the walls encroaches on the air spaces to a

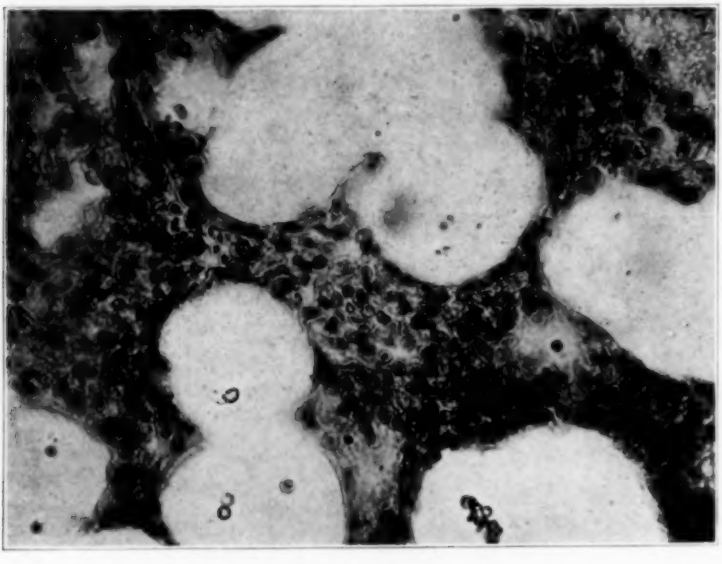

Fig. 2.—High power view of lung of mouse 2. Shows interstitial character of hemorrhage.

varying extent, often to the point of obliteration, so that such an area becomes consolidated almost completely, showing only here and there a small round vesicle that still contains air. The margins of such an area show the alveolar structure persisting but with greatly thickened walls (Fig. 2). The unaffected tissue about such an area is composed of greatly dilated infundibula with thin walls. The hemorrhage can be shown to be distinctly interstitial in character by the persistence in many cases of the lining epithelium of the air spaces (Fig. 2). In this stage the bronchi show desquamation of

their epithelium and frequently contain red blood cells (Fig. 3). There is a notable absence of any infiltration by polymorphonuclear leukocytes.

A slightly later stage of the process shows the breaking down or lysis of the erythrocytes in the alveolar walls. This can be traced from well preserved cells through gradual diminution of distinctness of outline and intensity of stain to a stage in which shadows only of the cells are seen, and finally only a hyalin eosin staining substance remains.

In this process the pigment of the cells is liberated and is seen free in the walls and also to a great extent taken up by large mononu-

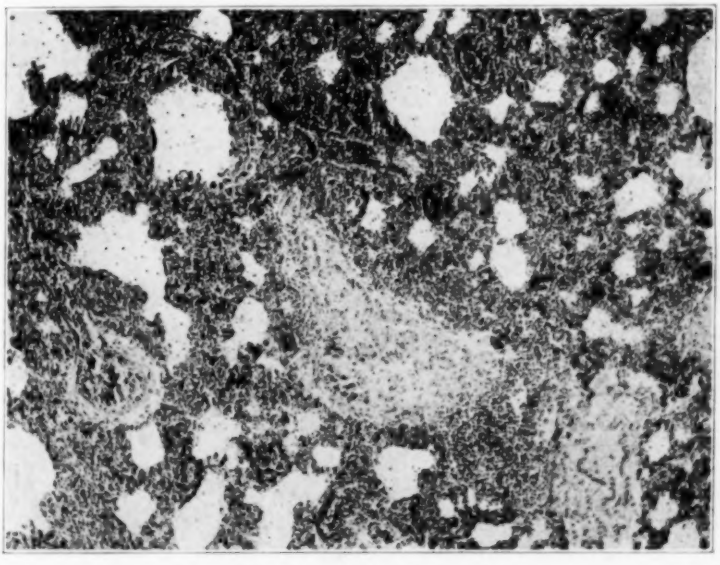

Fig. 3.—Low power view of lung of rabbit 84 C. Shows diffuse interstitial hemorrhage, and occlusion of bronchi by desquamated epithelium.

clear cells, perhaps endothelial leukocytes. Parallel with this process is the appearance in the thickened walls of an increasing number of mononuclear elements of various sizes. Some seem to be lymphocytes, others with oval vesicular nuclei suggest young connective tissue cells. Polymorphonuclear cells are not seen. The compressed air spaces during this stage may contain the same cellular elements as earlier, but in addition, in some part of almost every section, there is seen lining the alveoli a hyalin substance which appears to be closely adherent to the alveolar walls (Figs. 4 and 5). Some alveoli may be filled completely by it, others still contain one or more bubbles of air. The

usual condition, however, is to find a layer coating the wall. The condition suggests the exudation into the alveoli of a viscous, tenacious semifluid substance which takes its form from that of the vesicle containing it under the influence of the respiratory movement of air. This substance does not give the reaction of fibrin with the Weigert stain. It is usually stained faintly with eosin but in eosin-methylene blue preparations it is slow to give up the blue and unless differentiation is carried to completion it retains the blue color.

This substance differs from an ordinary edema fluid in its hyalin appearance and in its distribution. In fixed preparations coagulated

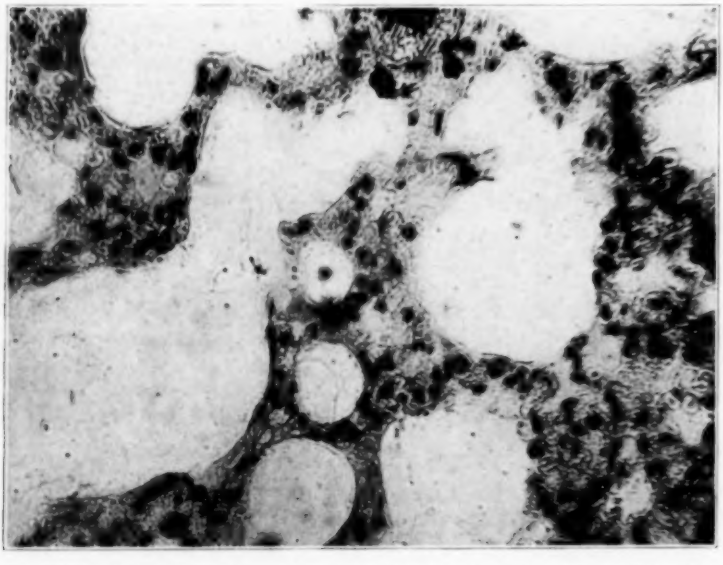

Fig. 4.—High power view of lung of rabbit 396. Shows infiltration of thickened alveolar walls by mononuclear cells, and deposit of hyalin membrane in alveoli.

edema fluid usually shows as a somewhat contracted cast of the alveolus, separated from the walls. This hyalin material is always closely applied to the wall of which it appears to be a part. Its origin is not clear, but certain sections have suggested that it may represent altered blood, exuded as such into the alveoli, there to undergo the same lytic change as already described for the blood in the alveolar walls. We have been able to trace the process with some distinctness through the gradual disintegration or disappearance of the red cells to the hyalin substance as described. In sections of this stage of the process the bronchi are often plugged completely with desquamated

epithelium, red cells and granular detritus. There is a notable increase of the peribronchial adenoid tissue, and focal accumulations of lymphoid cells occur about the larger blood vessels (Fig. 6). Occasionally, such a focus appears to be unrelated to bronchus or vessel. Several times we have observed the infiltration of the bronchial mucosa by these small round cells which penetrate the muscularis and lie between the columnar epithelium or in some cases displace the epithelium with the formation of small ulcers. The lymphatics throughout the section are enormously dilated and contain a hyalin substance similar to that found in the air cells with a few lymphocytes. When

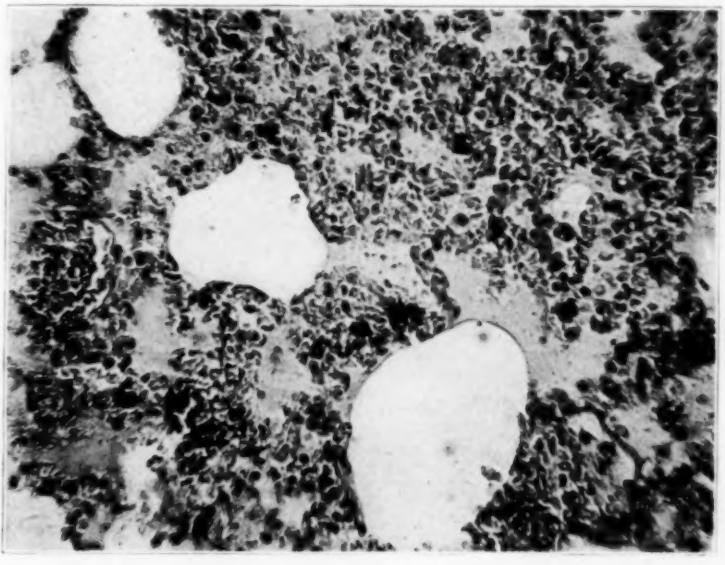

Fig. 5.—High power view of lung of rabbit F. Shows hemorrhage, interstitial and intra-alveolar, deposit of pigment, catarrhal exudation and presence of hyalin substance in alveoli.

pigment is present in the alveolar walls, the majority of specimens show the presence of eosinophil cells, usually mononuclear.

In cases that showed a superficial area of red coloration extending a short distance into the parenchyma of the lung, the microscope shows this to be due to an area of atelectasis doubtless caused by the obliteration or plugging of the bronchus supplying the area. The actual lesion itself is not apt to be subpleural, though these areas of atelectasis frequently give that impression in the gross.

In a few instances the hemorrhagic tendency has been so marked that the blood has escaped at once into the alveoli instead of being

confined to their walls. In such cases, however, the margins of the affected area show the usual interstitial arrangement in a way similar to the corresponding stages of pneumococcus infection, as shown by Blake and Cecil.[5a] Another interesting condition is the presence in many cases of thrombi of hyalin material in good sized blood vessels. In these, as well as in the alveolar walls, and in the air spaces, it has seemed possible to trace the transformation of blood to the hyalin substance through the intermediate stages.

Aside from blood and the hyalin substance the alveoli showed no marked exudate in most cases. In the more severe cases, however,

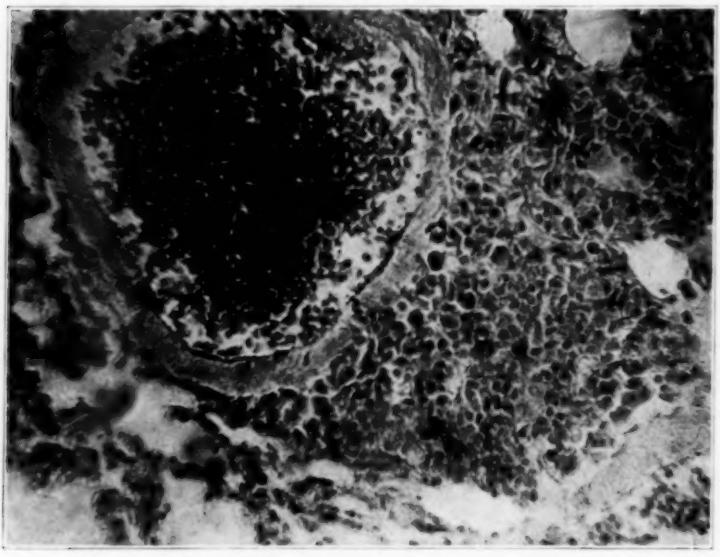

Fig. 6.—High power view of lung of rabbit 388. Shows blood vessel with hyalin degeneration of media and focus of lymphoid cells.

numbers of large mononuclear cells were present in most alveoli. These had the appearance of swollen and desquamated epithelium. In one fatal case large areas of the lung showed the alveoli filled with cells of this type so that at first glance it resembled gray hepatization. The intervening alveoli were completely filled with blood. Edema has been a rare finding. In one or two cases, however, it has been present. Fibrinous exudation in the alveoli has not been observed. In the two cases showing pleuritis fibrin was present in the exudate

5a. Blake, F. C., and Cecil, R. L.: J. Exper. M. **31**:445, 1920.

in small amount. Polymorphonuclear cells were also present in the pleuritic exudate with about an equal number of mononuclear cells.

The further evolution of the process is one of organization of the hemorrhagic areas. The number of nucleated elements in the thickened alveolar walls increases, the eosin-staining matrix resulting from the lysis of the red cells disappears, pigment is no longer seen and ultimately the areas are converted into scarlike connective tissue which still, however, shows the form of the thickened alveolar walls with alveolar spaces of reduced size (Fig. 7). Blood vessels and bronchi involved in this formation are compressed and atrophic. The nodular

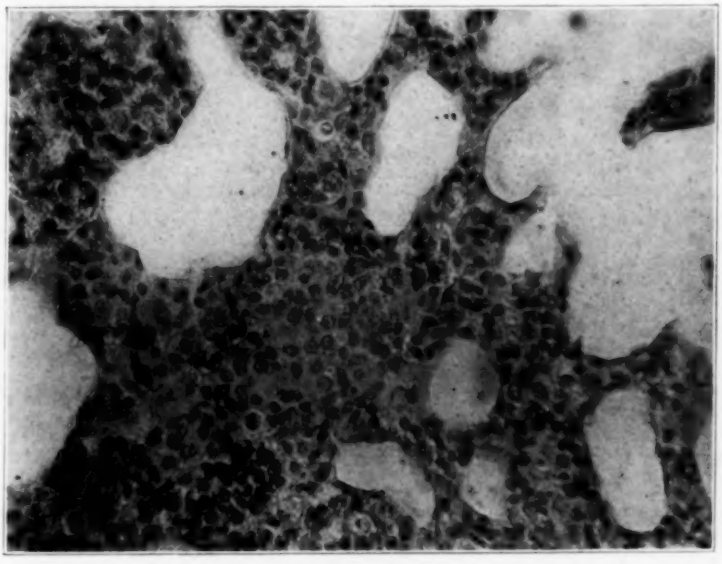

Fig. 7.—High power view of lung of guinea-pig 7. Shows carnification of thickened alveolar walls.

accumulations of lymphoid cells are no longer seen. The intervening lung tissue is even more expanded and emphysematous than was the case in the acute stages.

In organs other than the lungs, the same tendency to congestion and hemorrhage is found, and in addition, in parenchymatous organs, degeneration of epithelium. Except in the lung, lymphoid infiltration is rare.

The liver has usually been dark in color and dripped blood on section. Such organs showed microscopically dilatation of their blood vessels, usually most marked in the capillaries. In some cases a yellow

mottling of the surface was seen which was due to fatty change in the cells. Still other cases showed in addition to the congestion an extreme degenerative change in the liver cells. There was a transformation of the cytoplasm into coarsely granular material, and later its disappearance so that in the most advanced cases the cell consists of a membrane containing a well preserved nucleus, but apparently without cytoplasm. Focal necroses were not observed, except in cases showing secondary infection.

In the kidney a similar change was seen in the cells of the convoluted tubules. They were swollen and granular and occluded the lumen and especially under the capsule the cells were disintegrated, though never to the extent observed in the liver. Intertubular edema, marked cortical congestion and sometimes hemorrhage, were frequent findings. In one case intertubular infiltrations with lymphoid cells were found. The glomeruli were frequently somewhat contracted and the capsular epithelium swollen, in some cases distinctly cuboidal. Tubules and capsule often contained granular precipitate.

The spleen in early cases was usually large, soft and pulpy. The malpighian bodies were well preserved but the remainder of the organ was intensely hyperemic or hemorrhagic with blood pigment often present. Spleens from later cases were smaller and harder; the lymphoid elements of the pulp were much reduced and replaced by large mononuclear cells and fibroblasts.

The bronchial lymph nodes were regularly enlarged and dark red in color. Microscopically, they showed congestion and dilatation of the blood channels with widening of the marginal sinuses which frequently contained red blood cells. In animals injected subcutaneously the regional lymph nodes at the point of injection showed marked changes of the same character.

The brains of a few animals were examined and showed congestion and occasionally perivascular hemorrhage but no leukocytic infiltration.

The testes showed degenerative changes, loosening and separation of the cells of the tubules and in some cases cessation of spermatogenesis. In all organs hyalin degeneration of the walls of blood vessels is occasionally seen.

The essential feature of the process appears to be an injury of the walls of the blood vessels, especially the capillaries, evidenced by congestion and leading to hemorrhage. In the lungs this process is primarily interstitial or limited by the lining membrane of the alveoli, except in cases of exceptional severity when the blood is freed into the air spaces. There is no evidence of polymorphonuclear reaction, and except in cases of secondary infection purulent exudates do not

occur. Lymphoid infiltration is conspicuous in some stages of the process. This occurs in the thickened walls of the alveoli with the disappearance of the red cells, is frequent about the larger blood vessels and the normal peribronchial adenoid tissue is often increased and may infiltrate and even destroy portions of the bronchial mucous membrane. The secondary changes in the hemorrhagic exudate are of interest. The cells undergo lysis, passing first into a "shadow" stage and later into a hyalin eosin-staining mass. This process may give the explanation of the hyalin membrane lining the alveoli which is frequently observed. It may also account for the frequent finding of hyalin thrombi in the blood vessels. The hemorrhagic tendency is not limited to the lungs as hemorrhage has been seen in the liver, kidney, spleen, brain and voluntary muscle. The liver and kidney also show marked parenchymatous degeneration.

CONTROL EXPERIMENTS

The sputum from five different patients with noninfluenzal conditions was injected into twelve animals. These experiments were consistently negative and failed to show any lesions in any way resembling those described. The cases selected were of acute and chronic pulmonary and bronchial affections sent to the laboratory for examination for tubercle bacilli. This work was not done until two months after the height of the epidemic as it was felt that during the prevalence of the influenza it would be impossible to feel assured that the sputum did not contain the infective agent even in the absence of symptoms.

That the lesions are not produced by the injection of lung extracts is shown by one experiment in which the lung of a normal rabbit was emulsified, filtered and injected into a rabbit and a guinea-pig with negative results. That anaphylaxis or specific cytolysins might enter into the matter seemed possible, but at no time in the passage experiments has the lung extract of one animal been injected into one of another species and the lung of the latter injected into a member of the former species. The continuance of the process through nine animal passages would effectually rule out the possibility of a soluble toxin in the original sputum being responsible for the changes.

The attempt was made three times to control the injections by heating the portion of lung emulsion injected into one of the animals. Once the filtrate was boiled momentarily, once heated for two hours at 56 C. and once for one-half hour at the same temperature. All three of these cases showed positive lungs at the necropsy. It would thus appear that the agent responsible for the changes is not easily destroyed by heat.

TECHNIC

Sputum was collected in sterile containers from early cases of apparent severity. Microscopic examination in all cases showed the presence of a variety of organisms including pneumococci, streptococci, and small gram-negative bacilli. No attempt was made to isolate the various bacteria observed. The sputum was ground with sand in a sterile mortar diluted with several volumes of 0.85 per cent. saline solution and filtered through a Berkefeld or Mandler filter. The filters used were in all cases previously tested for their ability to retain the Pfeiffer bacillus and were shown to be in good condition. The filtrates were in every case cultured before injection into animals. The medium used for this purpose was the heated horse blood agar successfully used in the laboratory in the cultivation of the Pfeiffer bacillus, and which is also a good substrate

for the growth of all the known bacteria usually affecting the lung. In all cases these cultures remained sterile after a week's incubation. In several of the earlier experiments cultures were also kept under anaerobic conditions with like results.

Filtration was done directly into a plugged test tube which was sterilized with the filter and only opened after filtration, when a fresh sterile plug was at once inserted. Filters and tubes were sterilized in the autoclave under fifteen pounds pressure for thirty minutes. Filtration was always started under a negative pressure of not more than fifty millimeters of mercury. The filters usually clogged to some extent very quickly and more pressure was used in most cases before the necessary amount passed through. The rate of filtration never exceeded ten or fifteen drops per minute and was often much slower than that.

Needles and syringes used for injections were freshly boiled. Injections were made intravenously and subcutaneously in rabbits, subcutaneously in guinea-pigs and mice. In killing animals for examination, every care was taken to avoid any injury to the lungs. The best method is, perhaps, a blow in the cervical region producing immediate death. However, chloroform does not appear to alter the picture in any way.

In dissecting the animals the trachea was first exposed and clamped in order to avoid the possibility of entry of blood from severed vessels.

The lungs of affected animals were cut into small pieces after examination, grouped in a sterile mortar, the pasty mass suspended in saline solution, centrifugated lightly and filtered with the same precautions as were used for the sputum. In every case the filtrate was tested for sterility by culture methods before injection and was in every case sterile as far as that method is capable of determining.

Except in the cases noted otherwise, the lungs of all these animals were negative bacteriologically when examined. The heated horse blood agar was used as a routine medium for this purpose also.

Tissues for microscopic examination were fixed in 10 per cent. liquor formaldehydi or in Zenker's fluid and stained with hematoxylin and eosin, methylene blue, eosin and for bacteria with the McCallum-Goodpasture stain.

DISCUSSION

We have been able to produce in the animals used pulmonary lesions of a uniform type by injections of bacteriologically sterile filtrates from the sputum of five patients actually ill with influenza. A like number of experiments identically conducted but using sputum from patients in whom influenza could be excluded were entirely negative. We have been able to produce the same type of lesion in other animals by the injection of bacteriologically sterile filtrates of emulsions of the lungs of the animals first affected. This process can apparently be continued indefinitely. In view of these results, it seems justified to assume that we have been dealing with a living organism or virus, capable of passing through the filters used, which gives no visible growth on the culture medium employed, and which is able to induce in animals lesions of the type described. That these lesions were formed by a preformed toxin present in the patient's sputum seems definitely excluded in view of the passage through a long series of animals. The lesion is not the result of the injection of lung extract as is shown by the injection of filtered emulsions of the lungs of

normal animals as well as the occasional occurrence of negative results in our series. Experiments in cultivation of this "virus" have led us as yet to no definite conclusions, and until it is cultivated it is not possible to satisfy Koch's requirements for the demonstration of the relation of the organism to the disease.

If, however, it can be shown that the lesions developed in the course of this work can be harmonized with those accepted as characterizing the organs of patients dead of influenza, it would appear to be confirmatory of the claims of those writers who have advanced the "filtrable virus" as the primary cause of the disease. To obtain a basis of comparison it is necessary to consider the fact that in fatal cases of influenza in man there is present almost invariably infection with one or the other of the well known bacteria which have for years been associated with pulmonary inflammations in the absence of influenza. In one locality one form is found almost to the exclusion of others; in another locality a totally different form is found. This must be admitted in spite of the facile assumption of some authorities that failure to isolate the Pfeiffer bacillus has been due to the use of improper technic. It is natural, then, that the pathology, gross and microscopic, as described by different observers should vary to a considerable extent. Two methods appear available for determining the essential characters of the influenza lung. One method is to correlate the findings that are common to all groups of cases reported during the epidemic, irrespective of the organism reported as present, or the points in which such lesions differ from those usually produced by the same organism; the other method is to determine the findings that characterize those fulminant early cases which end in death before secondary infection could be much of a factor; those cases that failed to show bacteria on lung culture, or in which the bacteria, if present, were shown to be in such small numbers as to raise some doubt as to their relation to the process.

Reference to the recent literature gives sufficient data from cases of these classes to enable one to form a fairly comprehensive picture of the essential lesions of the primary influenza infection. One of the most comprehensive recent accounts of the pathology of influenza is contained in the study of a large series of necropsies at Camp Zachary Taylor during the 1918 epidemic, by Lucke, Wight and Kime.[6] They classified their cases into different types and found one type predominating in the early days of the epidemic and in those cases that ended in death after a relatively short illness, and they advance the view that this type represents most nearly the lesions of the primary virus. This type of lung is characterized by dark red or

6. Lucke, Wight and Kime: Arch. Int. Med., **24**:154 (Aug) 1919.

purplish mottling externally, the anterior edges of the lung frequently being emphysematous. The upper lobes are involved as frequently as lower. The cut section is dark, moist and exudes a bloody fluid. Areas of consolidation blend into the surrounding tissue rather than being sharply marked. Microscopically, hyperemia, hemorrhage and catarrhal exudation are the outstanding features. The capillaries are hugely dilated and frequently contain conglutination thrombi. The exudate is catarrhal with admixture of a large proportion of red cells. Polymorphonuclear cells are rare. There is desquamative bronchitis and bronchiolitis. Hyalin or conglutinative thrombi are found even in good sized vessels. In older cases evidence of carnification is seen. The trachea shows a hemorrhagic inflammation in these cases and usually contains bloody froth. The pleura is frequently involved in fatal cases, the exudation being of all types from serous to purulent. Cytologically, the pleural exudate contains large mononuclear cells with an admixture of polymorphonuclears. All observers agree that hemorrhage is a marked and early feature. Goodpasture and Burnett [7] say: "Primary toxic injury to the pulmonary tissue is a constant feature in the early stages of the pneumonia and presents a fairly characteristic picture. Alveolar walls are injured, capillaries ruptured and in places necrosed; there is an exudation of all the elements of the blood, larger or smaller areas of hemorrhage. Leukocytes are not especially prominent at this time and many are of the large mononuclear variety; and at this stage, organisms are comparatively few within the alveoli." They assume that the marked changes found in the lungs with so few bacteria are due to the toxin elaborated by bacteria in the upper air passages. This finding is, of course, as well explained by the assumption of an invisible infecting agent.

In speaking of early cases Wolbach [8] says: "the lungs are partially collapsed, dark red, lax but meaty in consistence. The pleural surfaces are often partly covered with dusky red mottling, due to small extravasations of blood beneath the pleural coat, . . . on section the lungs are dark red and wet, . . . on close inspection the surfaces are usually found to be thickly sprinkled with air vesicles of considerable size." Of the microscopic findings Wolbach says that the distinctive feature is an "acute alveolar emphysema, with the deposit of a hyalin fibrinous substance on the alveolar walls, the intervening alveoli are compressed and filled with exudate, which in the early stages is largely serous or bloody." The hyalin fibrin "outlines cavities filled with air which may or may not completely fill groups

7. Goodpasture, E. W. and Burnett, F. L.: U. S. Naval Med. Bull., **2**:177, 1919.

8. Wolbach, S. B.: Bull. Johns Hopkins Hosp., **30**:104, 1919.

of alveoli." While Wolbach does not mention the interstitial character of the hemorrhage in these early cases, his Figure 5, "a low power photomicrograph from an uncomplicated early influenza pneumonia," suggests very strongly this type of lesion.

Lecount [9] emphasizes the hemorrhagic character of the condition and draws special attention to the necrosis of the pulmonary capillaries. Oberndorfer [10] found marked hemorrhagic infiltration and later catarrhal or purulent exudate. W. G. McCallum [11] reports that the lesions found in early cases and especially in those showing the Pfeiffer bacillus on culture, suggest those described by him in the postmeasles pneumonias of the winter of 1917-1918 in army camps. (In this connection it is interesting to note, in passing, that many of these cases showed no history of recent measles and that Howard and Love [12] have expressed the opinion based on a study of the army statistics for 1917 and early 1918 that we had influenza with us in a mild form for more than a year before it assumed epidemic proportions). The distinctive feature of the postmeasles pneumonia as shown by McCallum was the interstitial location of the lesion. In the influenza cases he, too, has noted the hyalin substance lining the alveolar walls, and says that it does not give the reactions of fibrin. All these observers note a tendency to healing by organization which is seen even in fatal cases. P. J. Walker [13] describes the pathology of influenza, independently of the organism found in culture as "primarily an acute hemorrhagic lesion, interstitial or massive in extent."

It would appear, then, that the essential pathology of the influenza lung, unmodified by secondary infection, consists in an injury to the capillary walls resulting in congestion and hemorrhage, frequently interstitial, with obliteration or compression of some alveoli and emphysematous dilatation of others, leading in severe cases to intra-alveolar exudation of blood or serum, with little, if any, reaction on the part of the polymorphonuclear leukocytes, and with a tendency to healing by organization. There is described a characteristic hyalin membrane coating the walls of the alveoli in the neighborhood of the hemorrhagic lesions and in some cases completely filling the alveoli. Catarrhal exudation in alveoli, and especially in the bronchi, is described. Interstitial cellular reaction would appear to be lymphocytic. There is a rather constant hemorrhagic inflammation of the trachea. Other changes appear to depend on the presence and activity of various secondary invaders and to vary somewhat with the organisms found.

9. Lecount, E. R.: J. A. M. A., **72**:650 (March 1) 1919.
10. Oberndorfer: Münch. med. Wchnschr., **65**:810, 1918.
11. McCallum, W. G.: J. A. M. A., **72**:720 (March 8) 1919.
12. Howard, D. C., and Love, A. G.: Mil. Surg. **46**:522, 1920.
13. Walker, O. J.: J. Lab. & Clin. Med., **5**:154, 1919.

A comparison of the process found in our animals with the summary of findings in influenza as deduced from the published reports leads easily to the conclusion that the two are essentially similar, if not identical. The character of the lung lesion is the same in its primarily hemorrhagic nature, in its frequently interstitial location, in the absence of polymorphonuclear reaction, in the presence to some degree of catarrhal exudation in the alveoli and to a marked degree in the bronchi, in the presence of the hyalin membrane and of intervening emphysema and in the tendency to a final stage of carnification. The tracheitis is common to both conditions. Of lesions of other organs found more or less constantly in our cases, the type of kidney change agrees well with that described by Lucke, Wight and Kime, as does the finding in the spleen, large and congested in the earlier cases, atrophic with deposit of pigment and the presence of large mononuclear cells in the later stages. We have one instance of empyema in a chronic case and one dry pleurisy in a case ending in early death. We have one instance of hemorrhage in a degenerated voluntary muscle.

That the lesions found may be modified by secondary infection in such a way as to produce a picture even more similar to that of the usual influenza lung is shown by the results in certain mice in which material contaminated with *B. aertrycke* was used. Mouse 1 was inoculated intraperitoneally with the lung filtrate of a rabbit, the fourth passage from the original sputum. After four days of illness the mouse was killed and examined. The lungs showed the familiar interstitial hemorrhagic lesion. Further passages from the lungs were also positive. The peritoneum was washed and the washings centrifugated at high speed for ten minutes. The supernatant fluid was injected into a mouse and produced hyperemia of the lung but no characteristic lesion. The sediment suspended in saline solution, injected intraperitoneally, killed the mouse in eleven days, the lungs showing interstitial hemorrhage, but in most places so masked by infiltration with large numbers of polymorphonuclear leukocytes that the hemorrhagic character was only recognizable in scattered areas. Both lung and peritoneum showed cultures of *B. aertrycke*. Unfiltered peritoneal washings from this animal injected subcutaneously into two more mice produced death promptly. One mouse which died after fifty hours showed a condititon comparable to that last described. The other mouse, succumbing after only thirty-six hours showed a marked hemorrhagic lesion of the usual type without polymorphonuclear infiltration. This animal seems to have died of the primary infection before secondary infection developed and is comparable to certain fulminant cases of influenza. The fact that *B. aertrycke* ordinarily shows no tendency to produce pneumonic lesions indicates that in these cases the primary infection had prepared the way for the bacillus, which at necropsy

would appear to have caused the interstitial pneumonia. The filtrate of the lung emulsion of this animal proved capable of continuing the passage of the original lesion.

After the completion of the work here recorded, Olitsky and Gates published a preliminary note [14] of work which in many ways parallels ours with apparently harmonious results. Their short description of lesions produced would appear to differ from those here described not more than the difference in method of inoculation could easily account for. Our results appear to show that the infecting material injected into the circulation has a special predilection for pulmonary tissue but is also able to produce similar lesions in other organs. While the bronchial route is the most probable one for infection in nature, we have no definite proof that such is the case, and it is interesting to show that the "virus" locates in the lungs selectively when introduced into the circulation.

CONCLUSIONS

1. It is possible, by the injection of bacteriologically sterile filtrates of sputum from early cases of influenza into the circulation to produce in animals lesions of a uniform type uncomplicated by the presence of demonstrable bacteria.

2. The lesions thus produced are characterized by hemorrhage, a peculiar lytic change in the effused blood resulting in a hyalin end product with the deposit of pigment, infiltration by small mononuclear cells and eosinophils and healing by carnification.

3. These changes are comparable to those reported by many observers as characterizing influenza in so far as primary lesions may be separated from those produced by secondary invaders.

4. Control experiments with noninfluenzal sputum and with extract of normal lung are negative.

5. By injection of filtrates of lung emulsion from infected animals, the same lesion can be produced in other animals and the passage apparently continued indefinitely.

6. These results seem to give support to the theory of a filtrable agent as the primary cause of influenza.

7. Certain experiments indicate that the active agent concerned is markedly resistant to heat, and probably is mainly intracellular in location.

I wish to acknowledge my obligation to Lieut.-Col. E. B. Vedder, for permission to undertake this work and for many valuable suggestions and much constructive criticism; also to First Lieut. H. R. Livesay for aid in the bacteriologic part of the work.

14. Olitsky, P. K., and Gates, F. L.: J. A. M. A., **74**:1497 (May 29) 1920.

CHRONIC BRADYCARDIA *

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Chronic bradycardia and its attendant cardiovascular phenomena present innumerable interesting problems. Many causes are ascribed to the slow heart; this results in a cumbersome and confusing classification. It may not be amiss briefly to summarize the causes generally accepted:

1. *Chemical Substances.*—The inhibitory action of the following substances is well known and warrants no discussion here: (a) The neutral non-nitrogenous glucosids and resins; the active principles of digitalis, squills, strophanthus and apocynum; (b) alkaloids such as erythrophlein, veratrin and aconitin; (c) biliary constituents, and (d) inorganic substances, such as barium salts and hydrates.[1]

2. *Stimulation of the Cardiac Vagus.*—Stimulation may be peripheral or central.

3. *Myocardial Disease.*—Involvement of the myocardium by disease (a) associated with lesions of the auriculoventricular bundle (complete heart block and delayed impulse transmission), and (b) without involvement of the bundle.

4. Certain physiologic reactions without cardiac damage.

5. *The early and late stages of asphyxia.*[2]

PHYSIOLOGY OF CHRONIC BRADYCARDIA

Slowing of the heart may occur (1) through stimulation of the cardiac vagus, and (2) through changes affecting the cardiovascular system independent of innervation influences.

Vagus Stimulation.—Stimulation of the vagus may be peripheral or central. The cardiac effect is four-fold: (1) the inhibitory influence slowing rate (negative chronotropy); (2) the diminishing strength of contraction (negative inotropy); (3) the diminishing irritability (negative bathmotropy), and (4) the diminishing conductivity (negative dromatropy).[3] Bradycardia resulting from vagus influences is not permanent.

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* From Section on Medicine, Mayo Clinic.

1. Sollmann, T.: A Text-Book of Pharmacology. Philadelphia, W. B. Saunders Company, 1908, p. 477.

2. Konow, H. G. and Stenbeck, T.: Ueber die Erscheinungen des Blutdruckes bei Erstickung. Skand. Arch. f. Physiol., **1**:403, 1889. Quoted by Hirschfelder, p. 38.

3. Eppinger, H. and Hess, L.: Vagotonia. A Clinical Study in Vegetative Neurology. Nervous and Mental Disease Monograph Series No. 20. New York, Nervous and Mental Disease Publishing Co., 1915, pp. 14-15.

Changes Affecting the Cardiovascular System Independent of Innervation Influences.—The degree of cardiac filling and hence the volume outflow for each beat is directly modified by rate. Filling occurs during diastole and therefore the duration of diastole which is determined by rate, directly influences the volume outflow of blood.

The diastolic period is divided into two parts: (1) diastole proper, during which the filling of the ventricles is effected, and (2) diastasis, the period during which little or no filling occurs. "The greatest amount of output in unit time occurs at a rate which just allows the phase of diastolic filling to be complete but in which the next beat occurs before diastasis sets in. Any rate above or below this brings about some slowing of the circulation." [4]

Slowing of the heart rate below the point where adequate circulation is maintained due to diminished volume outflow per each beat as affected by rate, is cared for by other factors. An early attempt to increase volume outflow is by increasing contraction amplitude. This is not only revealed in the cardiac mechanism, but also in the effect on the general circulation. These circulatory phenomena are found in blood pressure studies, in the elevation of pulse pressure beyond normal limits.[5] The increase of pulse pressure is due largely to elevation of the systolic blood pressure. This cardiovascular status predisposes to ventricular hypertrophy, particularly of the left ventricle, another factor favoring increased volume outflow.

The systolic pressure represents essentially the strength of the heart beat. Its elevation, provided rate remains low and peripheral resistance constant, means complete ventricular filling and the subsequent expulsion of a large mass of blood. The diastolic pressure, other factors remaining constant, indicates the degree of peripheral resistance. It is logical, therefore, to argue that with the rate remaining low, the peripheral resistance remaining constant, the systolic pressure elevated and the diastolic pressure remaining normal, the increased pulse pressure represents increased volume outflow of blood. Add to these events an increased peripheral resistance and one of several phenomena results:

1. The heart rate remaining slow, a marked increase in both systolic and diastolic pressures occurs, resulting in a large pulse pressure. The degree of this reaction depends on the heart rate and the degree of peripheral resistance. This reaction is indicative of an increased volume outflow of blood.

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4. Hirschfelder, A. D.: Diseases of the Heart and Aorta. Philadelphia, J. B. Lippincott & Co., 1918, p. 11.
5. Plummer, H. S.: Personal Communication.

2. The heart rate accelerating and elevation of systolic pressure and greater elevation of diastolic pressure with a relatively smaller pulse pressure than in the preceding reaction is also evidence of increased volume outflow. In this instance the increased volume outflow is effected not only by increased amplitude of contraction but also by increased frequency of contraction.

When contraction amplitude diminishes, the rate accelerates and both systolic and diastolic pressures fall with diminution in pulse pressure. This phenomenon occurs when myocardial disintegration supervenes and as heart failure begins several additional factors come into play. With circulatory failure slowing of the circulation occurs, and there is a tendency to increase venous pressure which favors cardiac overdistention, predisposing to dilatation. This results in an increased carbon dioxid blood content which diminishes the tonicity of the heart muscle [6] thus further favoring dilatation. Cardiac dilatation implies diminished contraction amplitude, resulting in rate acceleration in the attempt to maintain adequate circulation.

Thus far my discussion has involved only the secondary effects of a primary bradycardia. Primary alterations of cardiovascular balance producing secondary bradycardia will be considered.

A cardiovascular system which has been subjected to increased demand for a relatively long period becomes an over-efficient mechanism when the demand is decreased. This statement must be modified in definitely excluding myocardial disintegration. Hypertrophy of the left ventricle is usually evident.

As circulatory demand is lowered, volume outflow is controlled by cardiac slowing also accompanied by circulatory changes. Pulse pressure is increased again by elevation of the systolic pressure.

These phenomena are observed in the over-efficient heart of the athlete after he assumes sedentary life, in certain cases of hyperthyroidism after the basal metabolic rate has attained normal and after the return to normal of a hypertension maintained for a time. Again, I wish to exclude the element of heart failure.

Another physiologic reaction often attended by bradycardia is observed frequently in typical myxedema and hypothyroidism, and is the manifestation of functional sluggishness resulting from a lowered basal metabolic rate. Pulse pressure is usually small, resulting from a lowered systolic pressure and is indicative of diminished volume blood outflow.

To summarize the physiology of bradycardia; several factors are involved: (1) The effect of vagus stimulation, and (2) changes affect-

6. Cameron, P. D.: Physiological and Pharmacological Studies on Cardiac Tonicity in Mammals, Johns Hopkins Hosp. Rep. **16**:549 1911.

ing the cardiovascular system independent of innervation influences; (*a*) the secondary effects of a primary bradycardia, and (*b*) primary alterations of the cardiovascular system producing a secondary bradycardia.

CLINICAL OBSERVATIONS

This study comprises 277 patients with bradycardia. The cases were grouped according to rate; ten point pulse differences determined this classification. The upper limit of pulse rate chosen was sixty beats for each minute. The cases were further subdivided into groups: (1) Those with myocardial disease; (*a*) with lesions of the auriculoventricular bundle, and (*b*) without involvement of the bundle; (2) endocardial valvular disease (this group obviously overlaps the previous group but to render it pure, was clearly separated), and (3) vagus augmentation.

Chronic Bradycardia Associated with Myocardial Disease.—This group is exclusive of complete heart block (complete auriculoventricular dissociation). All the patients presented definite evidence of myocardial disease.

Wilson,[7] in an interesting manner, has called attention to the changes affecting the myocardium in later life. He discusses the hardening of tissues by fibrosis as age advances and the effect of this senile degenerative process on the myocardium. The myocardium loses its normal resilience and becomes relatively "rigid."

The physiologic reactions of a myocardium with diminished elasticity and resilience resulting from sclerotic degeneration are extremely interesting. That the sclerosis often involves all the tissues of the heart and the functional interference of cardiac action by a relatively rigid pericardium is obvious.

Diminished elasticity implies diminished amplitude of contraction favoring under-filling and decreased volume outflow. To favor greater filling of the heart, rate is slowed, thereby increasing diastole. If this train of events progresses without increasing contraction amplitude, volume outflow becomes reduced to the point where the syndrome of cerebral anemia occurs. This reaction explains those cases presenting the Adams-Stokes syndrome unassociated with lesions of the auriculoventricular bundle and in which vagus augmentation is not present as determined by atropin response. I have had the opportunity of studying four such cases. Neuhof[8] has called attention to the presence of bradycardia in cardiosclerosis, the prototype of this condition.

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7. Wilson, T. S.: Early Diagnosis of Heart Failure and Other Essays on the Heart and Circulation. New York, Wm. Wood & Co., 1915, pp. 70-142.

8. Neuhof, S.: Clinical Cardiology, New York, Macmillan Co., 1917, p. 99.

The relationship of vagus augmentation to bradycardia occurring with myocardial disease must always be borne in mind, especially in young patients.

The myocardial disease group, exclusive of complete heart block, comprised 152 patients. One patient, a man, 49 years old, presented subjective and objective findings leading to the diagnosis of cardiosclerosis. His average pulse rate was less than 40 each minute and at the time of his initial electrocardiographic examination it was 38. There was normal sequential auriculoventricular rhythm with no evidence of auriculoventricular dissociation at any time during the examination period. He gave no symptoms referable to cerebral anemia. Systolic blood pressure was 128 mm.; diastolic pressure was 64 mm.; pulse pressure, 64 mm.

TABLE 1.—ETIOLOGY OF MYOCARDIAL DISEASE

Rate from 40 to 50

Decade	Cases	Males	Females	Chronic Myocarditis	Syphilis	Hypertension With and Without Clinical Nephritis	Anemia	Cardiosclerosis	Coronary Sclerosis
21-30	1	1	0	1	1	0	0	0	0
31-40	4	2	2	3	0	1	0	0	0
41-50	3	1	2	2	0	1	0	0	0
51-60	8	8	0	0	0	4	1	2	1
61-70	5	3	2	1	0	3	0	1	0
71-80	1	1	0	1	0	0	0	0	0
Total	22	16	6	8	1	9	1	3	1
Percentage		72.7	27.3	36.3	4.5	40.9	4.5	13.6	4.5

Syphilis included with chronic myocarditis.

Rate from 40 *to* 50.—Twenty-two patients comprised this group. The apparent etiologic basis of myocardial involvement is noted in Table 1. Chronic myocarditis (36.3 per cent.) and myocardial degeneration accompanying the hypertension group (40.9 per cent.) occurred with greatest frequency. One patient had syphilitic myocarditis. The Adams-Stokes syndrome was not present in this group.

Table 2 summarizes the electrocardiographic findings. The infrequency of auricular fibrillation (4.5 per cent.) is interesting and due probably to the fact that as a group these patients have diminished myocardial irritability. There was no instance of arborization block. Three electrocardiograms revealed nodal rhythm presenting the likelihood of superimposed vagus action.

One-third of the patients had T-wave negativity in their electrocardiograms which are detailed in Table 2. In a recent publication [9] I called attention to the significance of T-wave negativity occurring in isolated and combined derivations of the electrocardiogram and to changes in contraction preponderance resulting from functional or organic myocardial fatigue as being responsible for the negativity. In this connection I wish to consider T-wave negativity as it occurs in the succeeding groups. In the total myocardial group, T-wave negativity occurred in 30 per cent. of the electrocardiograms; in the endocardial valvular group it occurred in 14.2 per cent. and in the vagus group in only 7.4 per cent. This tapering occurrence as the normal myocardium is reached further supports my previous observations on T-wave negativity.

TABLE 2.—MYOCARDIAL DISEASE: ELECTROCARDIOGRAPHIC FINDINGS

Rate from 40 to 50

Decade	Cases	Sinus Bradycardia	Sinus Arrhythmia	Premature Contraction	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant Q R S in Derivation III	T-Wave Negativity			Ventricular Preponderance		
									Derivation I	Combined Derivations II and III	Derivation III	Left	Right	None
21–30	1	0	1	0	0	0	0	0	0	0	1	1	0	0
31–40	4	1	1	2	1	0	0	0	0	0	0	3	1	0
41–50	3	3	0	0	0	0	0	0	1	0	0	2	1	0
51–60	8	5	0	2	0	1	0	2	0	1	3	3	1	4
61–70	5	2	1	2	0	1	0	0	0	0	0	0	0	5
71–80	1	0	0	1	0	1	0	0	1	0	0	1	0	0
Total	22	11	3	7	1	3	0	2	2	1	4	10	3	9

Preponderance of the left ventricle occurred most frequently (45.4 per cent.); no unbalance occurred next in order of frequency (40.9 per cent.), and preponderance of the right ventricle occurred in only 13.6 per cent. of the tracings. The blood pressure studies are charted in Table 3. Two groups were compiled, the one including all cases and the other excluding those cases with frank hypertension. The increased pulse pressure is evident in both groups, greater obviously in the complete group, but in both instances exceeding the average normal of 50 mm. (67 mm. and 57 mm., respectively). It is at once apparent that the increased pulse pressure occurs through eleva-

9. Willius, F. A.: Clinical Observations on Negativity of the Final Ventricular Wave T of the Human Electrocardiogram, in press.

tion of the systolic pressure. This group is small and, therefore, averages are open to criticism, yet they are borne out by the larger subsequent groups.

Rate from 50 to 60.—There were 129 patients in this group. Table 4 summarizes the apparent etiologic conditions. Chronic myocarditis (47.3 per cent.) and myocardial degeneration associated with the hypertension group (29.4 per cent.) were present with greatest frequency. Six patients had syphilitic myocarditis. Four patients had typical Adams-Stokes seizures in spite of the fact that the auriculoventricular bundle was not obstructed.

TABLE 3.—MYOCARDIAL DISEASE: BLOOD PRESSURE STUDIES

Rate from 40 to 50

Decade	Complete Group					Exclusive of Hypertension				
	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
21–30.....	1	144	90	54	50	1	144	90	54	50
31–40.....	4	135	80	55	56	2	99	63	36	48
41–50.....	3	109	79	50	48	2	143	73	70	47
51–60.....	8	142	84	58	45	6	136	81	54	46
61–70.....	5	196	87	109	45	1	160	75	85	47
71–80.....	1	122	70	52	46	1	122	70	52	46
Average..	22	156	80	67	48	13	133	77	57	47

TABLE 4.—MYOCARDIAL DISEASE

Rate from 50 to 60

Decade	Cases	Males	Females	Chronic Myocarditis	Syphilis	Hypertension With and Without Clinical Nephritis	Anemia	Cardiosclerosis	Coronary Sclerosis
21–30.....	3	2	1	2	0	1	0	0	0
31–40.....	16	14	2	14	1	2	0	0	0
41–50.....	28	21	7	17	4	7	1	2	1
51–60.....	38	33	5	14	0	10	2	4	8
61–70.....	38	35	3	12	1	16	1	3	6
71–80.....	6	5	1	2	0	2	0	2	0
Total.....	129	110	19	61	6	38	4	11	15
Percentage....	.....	85.2	14.7	47.3	4.6	29.4	3.1	8.5	11.6

The electrocardiographic findings in this group are recorded in Table 5. Auricular fibrillation occurred in only a few cases (3.1 per cent.). Twenty-one jatients (16.2 per cent.) had sinus arrhythmia indicative, possibly, of a superimposed vagus action. Arborization block (7.7 per cent.) and aberrant Q R S complexes in isolated derivations of the electrocardiogram (13.9 per cent.) were present in this

group, although not as outstanding occurrences. T-wave negativity was recorded in 30 per cent. of the electrocardiograms. Dominance of preponderance of the left ventricle (62.0 per cent.) was also present in this group. Right preponderance occurred in only 8.5 per cent. of the tracings and no unbalance was present in 29.4 per cent. Increased work for the left ventricle is the usual order in chronic bradycardia and agrees with the frequency of preponderance of this chamber as revealed by the electrocardiogram.

TABLE 5.—MYOCARDIAL DISEASE: ELECTROCARDIOGRAPHIC FINDINGS
Rate from 50 to 60

Decade	Cases	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Arborization Block	Aberrant Q R S in Isolated Derivation				T-Wave Negativity					Ventricular Preponderance			
							Derivation I	Derivation II	Combined Derivations I, and III	Derivation III	Derivation I	Combined Derivations I and II	Combined Derivations II and III	Combined Derivations I, II and III	Derivation III	Prolonged A-V Conduction	Left	Right	None
21-30	3	1	1	1	0	1	0	0	0	0	0	0	0	0	1	0	1	1	1
31-40	16	7	8	1	0	0	0	0	0	2	1	0	0	0	3	1	8	2	6
41-50	28	19	4	5	0	1	0	1	1	3	0	0	0	0	5	0	18	2	8
51-60	38	29	2	5	2	2	0	1	0	2	3	1	2	1	6	1	28	1	9
61-70	38	28	5	6	1	5	1	3	2	2	5	0	3	1	7	3	20	4	14
71-80	6	2	1	3	1	1	0	0	0	0	0	0	0	0	0	0	5	1	0
Total	129	86	21	21	4	10	1	5	3	9	9	1	5	2	22	5	80	11	38

TABLE 6.—MYOCARDIAL DISEASE: BLOOD PRESSURE STUDIES
Rate from 50 to 60

Decade	Complete Group					Exclusive of Hypertension				
	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
21-30.....	3	131	78	53	52	3	131	78	53	52
31-40.....	16	129	85	44	52	16	129	85	44	52
41-50.....	28	132	82	50	56	24	125	78	47	56
51-60.....	38	148	86	62	56	28	129	78	51	55
61-70.....	38	157	88	69	56	25	140	79	61	56
71-80.....	4	165	86	79	56	3	152	83	69	55
Average..	127*	145	85	60	55	99	131	79	52	55

* Two cases without blood pressure readings.

Table 6 presents the blood pressure readings. An increased pulse pressure is again noted, most marked in the complete group (60 mm.) but not much altered when the frank hypertension readings are excluded (52 mm.). The greater pulse pressure has probably the most accurate value as some of the hypertension readings were

undoubtedly associated with physiologic cardiovascular reactions, especially in those cases in which there were relatively high systolic and normal or slightly elevated diastolic pressures.

The theme of increased pulse pressure is maintained throughout chronic bradycardia.

COMPLETE HEART BLOCK (COMPLETE AURICULOVENTRICULAR DISSOCIATION)

I have observed twenty-two patients with complete heart block. The bradycardia associated with this disorder is due to failure of the auricular impulse to pass along the auriculoventricular bundle. Thus the ventricle is not excited to contraction by the impulses arising in the sino-atrial node but assumes an independent rhythm which is slow and often incoordinate. Permanent complete heart block is associated with disease of the auriculoventricular bundle obstructing impulse conduction, although cases in the literature are described in which no lesion was demonstrable.[10] Cases of transient complete heart block have been reported [11] and our records reveal two such cases.

The apparent etiologic conditions are tabulated in Table 7. Chronic myocarditis occurred in half the cases and chronic endocardial valvular disease and myocardial degeneration associated with the hypertension group in 22.7 per cent., respectively. One case of cardiosclerosis is recorded. Syphilis was not demonstrated in a single instance. Five patients were still free from Adams-Stokes seizures although the heart block was complete.

The blood pressure studies in this group are very interesting (Table 8). The average pulse pressure is large (97 mm.), a marked exaggeration of those in the preceding groups.

Generally, a high systolic pressure indicates strength of cardiac contraction plus adequate filling and emptying, provided the peripheral

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10. Hume, W. E.: A Case of Heart-block in which there was no Pathological Lesion of the Connecting Muscular System. Heart, **5**:149, 1913.

Krumbhaar, E. B.: Adams-Stokes' Syndrome, with Complete Heart-block, without Destruction of the Bundle of His, Arch. Int. Med., **5**:583, (May) 1910.

Pepper, W. and Austin, J. H.: Adams-Stokes' Syndrome, with Complete Heart-block and practically normal bundle of His, Am. J. M. Sc., **143**:716, 1912.

11. Cohn, A. E.: A Case of Transient Complete Auriculo-ventricular Dissociation, Showing Constantly varying Ventricular Complexes, Heart, **5**:5, 1913.

Cohn, A. E. and Lewis, T.: Report of a Case of Transient Attacks of Heart Block, Including a Post-mortem Examination, Heart, **2**:241, 1910.

Heard, J. D. and Colwell, A. H.: A Study of a Case of Intermittent Complete Dissociation of Auricles and Ventricles Presenting Unusual Features. Arch. Int. Med., 18:758 (Nov.) 1916.

Wilson, F. N. and Robinson, G. C.: Heart-block. II. Transient Complete Heart-Block with Numerous Stokes-Adams Attacks, Arch. Int. Med. **21**:181 (Feb.) 1918.

resistance remains constant, influenced, of course, as previously emphasized, by rate. The average systolic pressure was 12 mm. The average diastolic pressure was normal (75 mm.). This, again, illustrates that the increased pulse pressure occurs by elevation of systolic pressure.

TABLE 7.—COMPLETE HEART BLOCK

Decade	Cases	Males	Females	Endocardial Valvular Disease	Syphilis	Chronic Myocarditis	Hypertension With and Without Clinical Nephritis	Cardiosclerosis	Coronary Sclerosis
21-30	1	0	1	0	0	1	0	0	0
31-40	3	2	1	1	0	2	0	0	0
41-50	5	3	2	2	0	3	0	0	0
51-60	2	2	0	1	0	0	1	0	0
61-70	11	7	4	1	0	5	4	1	0
Total	22	14	8	5	0	11	5	1	0
Percentage	.....	63.6	36.4	22.7	.....	50.0	22.7	4.5	

TABLE 8.—COMPLETE HEART BLOCK. BLOOD PRESSURE STUDIES

Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Ventricular Rate	Auricular Rate
21-30	1	158	78	80	48	92
31-40	3	133	73	60	39	74
41-50	5	131	75	56	35	74
51-60	2	185	62	123	35	80
61-70	11	201	78	123	37	75
Average	22	172	75	97	37	76

Musser [12] reported two cases of high systolic pressures in complete heart block, and collected eighteen others from the literature. He also emphasizes increased blood outflow as follows: "This high pressure is dependent more on increased blood mass discharged by the left ventricle than on the associated cardiac hypertrophy and peripheral sclerosis." In our series, eight patients had systolic readings of 200 mm. and over.

That the large pulse pressure is indicative of increased volume outflow of blood is illustrated in the reactions following the administration of thyroxin [13] (thyroid active principle). In a previous publication [14] we reported the use of thyroxin (termed alpha-iodin at

12. Musser, J. H., Jr.: Heart Block Associated with High Blood Pressure. Arch. Int. Med. **20**:127 (July) 1917.

13. Kendall, E. C.: The Thyroid Hormone. Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, **9**:309, 1917.

14. Blackford, J. M., and Willius, F. A.: Chronic Heart Block, Am. J. M. Sc. **154**:585, 1917.

that time) in complete heart block, but no definite conclusions were reached as to the cardiovascular reactions involved. In 1915, Dr. H. S. Plummer suggested the use of thyroxin in complete heart block attended by Adams-Stokes seizures. In Dr. Plummer's observations of a great number of patients suffering with hyperthyroidism he found that the heart in hyperthyroidism delivers an increased output of blood each beat. The first patient subjected to thyroxin treatment was symptomatically relieved within two weeks, and remained free from the distressing manifestations of cerebral anemia almost three years, but ultimately died of myocardial disintegration.

Interesting changes in this patient's blood pressure readings were observed. On admission to the Clinic he was having from ten to fifteen Adams-Stokes seizures daily. At this time the systolic pressure was 112 mm., diastolic pressure 60 mm., and pulse pressure 52 mm. Subsequent blood pressure readings during the remaining years of his life showed increased pulse pressure readings due to elevation of systolic pressure. The readings were: systolic pressure, 142 mm., diastolic pressure, 64 mm., pulse pressure, 78 mm.; systolic pressure, 144 mm., diastolic pressure, 78 mm., pulse pressure, 66 mm.; and systolic pressure, 148 mm., diastolic pressure, 76 mm., pulse pressure, 72 mm. These records were taken during practically continuous thyroxin administration over a period of nearly three years. There was no appreciable change in ventricular rate, although the auricular rate accelerated slightly. The relief from the symptoms of cerebral anemia was, therefore, not due to ventricular rate acceleration but to increased volume outflow of blood. Subsequent cases have confirmed the findings in this case. Mackenzie's[15] observations have shown that ventricular standstill for ten seconds produces unconsciousness and for twenty seconds general convulsions of the body. It is obvious that marked diminution of blood outflow of the left ventricle, even without ventricular standstill, may produce cerebral anemia. The relief from thyroxin seems to bear this out. Thyroxin action in effecting increased blood outflow is two-fold: (1) by increasing basal metabolic rate, and (2) by increasing myocardial irritability.

CHRONIC BRADYCARDIA ASSOCIATED WITH CHRONIC ENDOCARDIAL VALVULAR DISEASE

This group is exclusive of complete heart block. It obviously overlaps the myocardial group but has been classified separately to maintain that group clearly. Two factors enter into the chronic bradycardia of this group: (1) myocardial changes (previously discussed), and (2) vagus augmentation.

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15. Mackenzie, Sir J.: Principles of Diagnosis and Treatment in Heart Affections. London, Frowde, 1916, p. 64.

Rate from 40 *to* 50.—There were only eight patients in this group. Six had mitral regurgitation, one mitral stenosis, and another a double mitral lesion. All patients had mild "decompensation." There was nothing outstanding in the electrocardiographic findings, which are summarized in Table 9. Preponderance of the right ventricle occurred in 62.5 per cent. of the cases and would be expected with the high incidence of mitral disease. There was no instance of left preponderance.

Table 10 summarizes the blood pressure readings. The pulse pressure is increased 57 mm. This again occurs through elevation of the systolic pressure.

TABLE 9.—ENDOCARDIAL VALVULAR DISEASE. ELECTROCARDIOGRAPHIC FINDINGS
Rate from 40 to 50

Decade	Cases	Males	Females	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant QRS in Derivation I	T-wave Negativity	Ventricular Preponderance: Left	Right	None
21-30	1	0	1	0	1	1	0	0	0	0	0	0	1	0
31-40	3	2	1	2	0	1	0	1	0	0	0	0	2	1
41-50	3	2	1	1	2	1	0	0	0	1	0	0	2	1
71-80	1	1	0	0	0	0	1	0	0	0	0	0	0	1
Total	8	5	3	3	3	3	1	1	0	1	0	0	5	3

TABLE 10.—ENDOCARDIAL VALVULAR DISEASE. BLOOD PRESSURE STUDIES
Rate from 40 to 50

Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
21-30	1	114	90	24	46
31-40	3	141	77	64	47
41-50	3	135	79	56	46
71-80	1	152	80	72	46
Average	8	137	80	57	46

Rate from 50 *to* 60.—Twenty-seven patients were recorded in this group. There were eleven with mitral regurgitation, two with mitral stenosis, four with double mitral lesions, eight with aortic regurgitation, one with double aortic lesion, and one with aortitis and aortic regurgitation. Syphilis was demonstrated in one patient. The electrocardiographic findings are found in Table 11. Preponderance of the left ventricle occurred most frequently (40.7 per cent.). The blood pressure readings are recorded in Table 12. The average pulse pressure is again increased—67 mm. If the blood pressure readings of the

patients having aortic regurgitation are eliminated, the modified average pulse pressure is found to be 58 mm., still greater than normal and due to elevation of the systolic pressure. This theme is reiterated throughout the whole series.

TABLE 11.—Endocardial Valvular Disease. Electrocardiographic Findings

Rate from 50 to 60

Decade	Cases	Males	Females	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant Q R S in Derivation I	T-wave Negativity					Ventricular Preponderance		
											Aberrant Q R S in Derivation III	Derivation I	Derivation III	Combined Derivations II and III	Combined Derivations I, II and III	Left	Right	None
11–20	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
21–30	6	5	1	2	4	1	0	0	1	0	0	0	1	1	0	2	3	1
31–40	10	8	2	5	5	0	0	0	0	0	0	0	0	0	0	5	1	4
41–50	5	3	2	3	1	0	1	0	1	1	0	1	0	0	0	1	0	4
51–60	4	3	1	3	0	0	1	0	0	0	1	0	0	0	1	2	0	2
61–70	1	1	0	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0
Total	27	21	6	15	10	1	2	0	2	1	1	1	2	1	1	11	5	11

TABLE 12.—Endocardial Valvular Disease. Blood Pressure Studies

Rate from 50 to 60

Decade	Complete Group					Exclusive of Aortic Regurgitation				
	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
11–20	1	138	64	74	56	1	138	64	74	56
21–30	6	145	78	67	58	5	142	86	56	58
31–40	10	131	67	64	57	8	125	71	54	57
41–50	5	129	65	64	54	1	126	78	48	56
51–60	3	154	79	75	57	2	136	68	68	55
61–70	1	140	68	72	53	0	0	0	0	0
Total	26*	137	70	67	56	17	133	75	58	56

* One case without blood pressure readings.

In aortic regurgitation the left ventricle contains more blood than normal, due to the regurgitation of blood backward from the arterial circulation, and thus it is able to contract with its maximal strength on a large volume of blood, giving rise to a relatively increased systolic pressure. The diastolic pressure is usually lowered, and the high pulse pressure results from the large swing affecting the arterial circulation due to the direct blood regurgitation back into the heart. The associated hypertrophy of the left ventricle aids in elevating systolic pressure. The large pulse pressure of aortic regurgitation thus differs from that of chronic bradycardia.

BRADYCARDIA OF VAGUS ORGIN

The effect of vagus augmentation on the cardiac mechanism varies greatly. The most frequent effect is transient slowing of the heart. Patients are encountered running slow heart rates and who may conveniently be grouped under the mysterious term of vagotonia. They are apparently healthy persons with neurotic tendencies, running slow heart rates which accelerate with the administration of atropin. In this group no evidence of organic heart disease was found and no subjective cardiac complaints, except in a few patients who were conscious of an extrasystolic arrhythmia.

TABLE 13.—VAGUS GROUP. ELECTROCARDIOGRAPHIC FINDINGS

Rate from 40 to 50

Decade	Cases	Males	Females	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant Q R S in Isolated Derivations	T-wave Negativity in Derivation III	Ventricular Preponderance		
												Left	Right	None
21-30	5	5	0	2	3	0	0	0	0	0	1	3	0	2
31-40	3	3	0	0	3	0	0	0	0	0	0	0	2	1
41-50	4	3	1	4	0	0	0	0	0	0	1	3	0	1
Total	12	11	1	6	6	0	0	0	0	0	2	6	2	4

TABLE 14.—VAGUS GROUP. BLOOD PRESSURE STUDIES

Rate from 40 to 50

Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
21-30	5	113	70	43	46
31-40	3	109	73	36	45
41-50	3	116	77	39	46
Average	11*	113	73	40	46

* One case without blood pressure readings.

Rate from 40 *to* 50.—There were twelve patients in this group. The electrocardiographic findings are found in Table 13. The blood pressure findings are interesting and contrast sharply those of the preceding groups (Table 14). The average pulse pressure is found to be 40 mm., about 10 mm. less than the average normal. This diminution is effected by a drop in the systolic pressure. It must be emphasized here that the bradycardia of vagus origin is not permanent and hence no permanent alterations in cardiovascular balance occur.

Rate from 50 to 60.—This group comprises fifty patients. The electrocardiographic findings are recorded in Table 15 and the blood pressure readings in Table 16. The average pulse pressure is 45 mm., and as in the foregoing group, slightly diminished rather than increased.

TRANSIENT VAGUS AUGMENTATION

Sino-Atrial Heart Block.—Sino-atrial heart block or transient cardiac standstill is rarely observed and is usually ascribed to vagus stimulation.[16] It, however, has been noted during the administration of digitalis,[17] salicylic acid,[18] aconitin [19] and morphin.[20]

The failure of the auricle to contract may result from (1) failure or weakness of impulse genesis, (2) muscle weakness, or (3) blocking of the impulse between the sino-atrial node and the auricle.

Our series contributes six cases of sino-atrial heart block to the literature and these cases are summarized in Table 17. The patients ranged from 12 to 61 years of age. In only one instance was there evidence of organic heart disease, and that in the oldest patient who presented the clinical findings of a frank myocarditis. In addition to the sino-atrial block, his electrocardiograms revealed delayed auriculoventricular conduction and transient complete heart block. The other cases could be ascribed only to vagus augmentation.

The average pulse rate in this series was 57 each minute. The average systolic pressure 141 mm., diastolic pressure 89, and pulse pressure, 52 mm.

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16. Brown, N. W.: Sino-Atrial Heart Block in a Child, with Observations on Effects of Atropin and Vagus Stimulation, Arch. Int. Med. **24**:458 (Oct.) 1919.

Eyster, J. A. E. and Evans, J. S.: Sino-auricular Heart Block, with Report of a Case in Man, Arch. Int. Med., **16**:832 (Dec.) 1915.

Eyster, J. A. E., and Meek, W. J.: Experiments on the Origin and Conduction of the Cardiac Impulse. VII. Sinoventricular and Sinoauricular Heart-Block. Arch. Int. Med., **19**:117 (Jan.) 1917.

Levine, S. A.: Observations on Sino-auricular Heart-block, Arch. Int. Med., **17**:153 (Jan.) 1916.

17. Hewlett, A. W.: Digitalis Heart Block. J. A. M. A., **48**:47 (Jan. 5) 1907.

Parkinson, J.: Digitalis in Soldiers with Cardiac Symptoms and a Frequent Pulse. Heart, **6**:321, 1915.

White, P. D.: Auricular Standstill: An Unusual Effect of Digitalis on the Heart, with Especial Reference to the Electrocardiogram. Boston M. & S. J., **175**:233, 1916.

18. Sicard, M. H. and Meara, F. S.: A Report of Three Cases Showing Vagus Influence. Am. J. M. Sc., **150**:843, 1915.

19. Cushny, A. R.: The Irregularities of the Mammalian Heart Observed Under Aconitine and on Electrical Stimulation, Heart, **1**:1, 1909.

20. Cohn, A. E.: The Effect of Morphin on the Mechanism of the Dog's Heart After Removal of One Vagus Nerve, Jour. Exper. M., **18**:715, 1913.

Eyster, J. A. E. and Meek, W. J.: Experiments on the Origin and Propagation of the Impulse in the Heart, Heart, **5**:137, 1913.

TABLE 15.—VAGUS GROUP. ELECTROCARDIOGRAPHIC FINDINGS

Rate from 50 to 60

Decade	Cases	Males	Females	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant QRS in Isolated Derivations	T-wave Negativity in Derivation III	Ventricular Preponderance		
												Left	Right	None
11–20	5	4	1	1	4	0	0	0	0	0	0	2	1	2
21–30	14	11	3	6	6	3	0	0	0	0	3	1	6	7
31–40	15	13	2	11	4	1	0	0	0	0	0	1	1	13
41–50	12	12	0	10	3	0	0	0	0	0	0	1	3	9
51–60	3	3	0	2	1	0	0	0	0	0	0	0	1	2
Total	50	44	6	30	18	4	0	0	0	0	3	5	12	33

TABLE 16.—VAGUS GROUP. BLOOD PRESSURE STUDIES

Rate from 50 to 60

Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
11–20	5	132	70	62	53
21–30	13	118	76	42	57
31–40	14	124	78	46	56
41–50	12	117	76	41	56
51–60	3	127	76	51	57
Average	47*	121	76	45	55

* Three cases without blood pressure readings.

TABLE 17.—SINO-ATRIAL HEART BLOCK

Rate from 50 to 60

Cases	Males	Females	Age, Years	Premature Contractions	Aberrant QRS in Derivation III	Aberrant QRS in Combined Derivations II and III	Prolonged Pulse Rate Interval	Complete Heart Block	T-wave Negativity in Derivation III	Ventricular Preponderance		
										Left	Right	None
1	1	0	12	0	1	0	0	0	0	0	0	1
1	0	1	33	0	0	1	0	0	1	0	0	1
1	0	1	39	0	1	0	0	0	0	0	0	1
1	1	0	46	1	0	0	0	0	0	1	0	0
1	0	1	57	0	0	0	0	0	0	1	0	0
1	1	0	61	0	0	0	1	1	0	0	0	1
6	3	3	..	1	2	1	1	1	1	2	0	4

Ventricular Escape.—Ventricular escape, a relatively rare disorder of the cardiac mechanism, is at times due to transient vagus augmentation. In this disorder, the ventricle occasionally escapes from the influence of the sino-atrial node through independent automatism of the atrioventricular node. Two types of ventricular escape occur:[21] (1) resulting from depression of the sino-atrial node so that the atrioventricular node asserts itself by virtue of its inherent automatism, and (2) resulting from increased irritability of the atrioventricular node. In the type resulting from vagus augmentation, the sinus rate is slow. One case of ventricular escape has been observed, apparently of vagus origin.

COMMENT

Chronic bradycardia is discussed, including physiologic reactions involved, and a consideration of various types of bradycardia and associated conditions.

21. White, P. D.: Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater than that of the Auricles, Arch. Int. Med., **18**:244, 1916.

Fifty cents each will be paid for the following issues of the Archives of Internal Medicine: January, March, June, August, 1918. January and July, 1916; November, 1915; January, 1911; July, 1909. AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.